PROLONGED LABOUR*

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MANY of us are old enough to remember the time when a serious disturbance of uterine activity in the first stage of labour nearly always resulted in the death of the baby, and sometimes of the mother as well. Once the diagnosis was established, labour had invariably been in progress for at least twelve hours, and cæsarean section was then outruled by the risk of fatal peritonitis. So the attendant had no option but to allow the labour to linger on. The only safe remedy available, as one 19th-century writer put it, was " tincture of time " (Eastman 1950). Meanwhile, the patient could be relieved with morphine, but sooner or later the baby died in utero. If by then the mother's condition was also causing anxiety, the fœtus was extracted, with or without embryotomy, and often through an incompletely dilated cervix. The obstetrician was well satisfied if the mother survived. The loss of her baby was accepted as inevitable and of little consequence; she could always have more children in the future—provided her fertility was not impaired by tubal infection or cervical damage.

Present-day obstetricians, armed with new knowledge and methods for combating infection, recognise that Nature and time are unreliable allies. Their attitude is governed by the dictum that it is unwise ever to allow the sun to set twice during any one labour. Yet ideas as to what constitutes dangerous prolongation of labour still vary. Some obstetricians consider that cæsarean section is indicated if labour is not completed in twenty-four hours, or if the membranes have been ruptured for twenty-four hours. Others have arbitrary time limits of thirty, thirty-six, or forty-eight hours before resorting to this operation. Although rules of this kind may have some background value, they cannot be made hard and fast without becoming farcical.

*Abridged from the Charter Day lecture given at the National Maternity Hospital, Dublin, on Jan. 28, 1961.

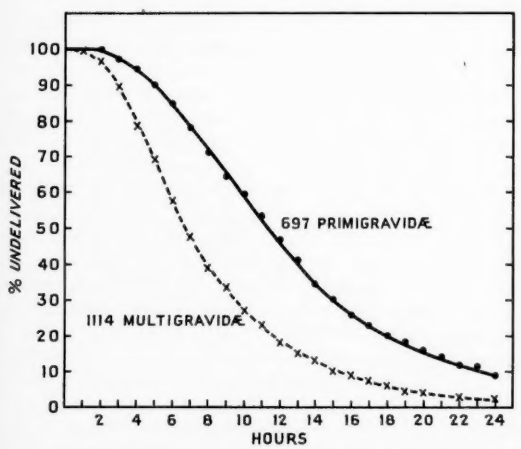

Fig. 1—The difference in duration of normal labour in primigravidæ and multigravidæ.
10% primigravidæ and 2·5% multigravidæ were undelivered at 24 hours. Labours completed by forceps delivery were included.

Duration of Normal Labour

In the first place, although averages of fourteen to eighteen hours for first labours, and of eight to twelve hours for second labours, are variously reported, there are wide individual differences within the limits of normal. This is well shown by a study of 1811 consecutive " normal " labours in Mill Road Maternity Hospital, Liverpool, during 1958–59 (fig. 1). By normal is meant labour completed vaginally (sometimes with the help of low forceps) in women taller than 5 ft. 1 in. and without evidence of contracted pelvis. Premature and postmature labours, multiple pregnancy, and fœtal malformation and malpresentation were excluded. 55% of primigravidæ and 80% of multigravidæ completed their deliveries within twelve hours. Nevertheless, 10% of normal labours in primigravidæ and 2·5% of normal labours in multigravidæ lasted longer than twenty-four hours. This only goes to show how difficult and arbitrary is the diagnosis of uterine inefficiency, or even of prolonged labour. The findings also illustrate the well-known but extraordinary difference in efficiency of the birth process in multigravidæ as compared with primigravidæ. Parturition is a function at which the genital tract becomes proficient only with experience; it becomes even more efficient with advancing parity. Thus, fig. 2 shows that labour tends to be slightly more rapid in women having their fifth and subsequent child than in those having their second, third, or fourth child. The uterus certainly does not become inert from frequent use. Nor is its action impaired by excessive distension. As I emphasised in 1938 (Jeffcoate 1938), and as is shown in fig. 3, the duration of labour in twin pregnancies for both primigravidæ and multigravidæ does not differ materially from that for single births. And when it is longer, the delay is nearly always between the delivery of the first and second twin.

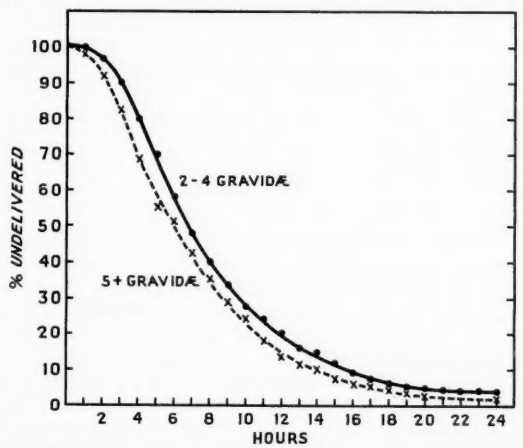

Fig. 2—The duration of labour according to multiparity, showing that women having their fifth or subsequent child have shortening rather than lengthening of labour.

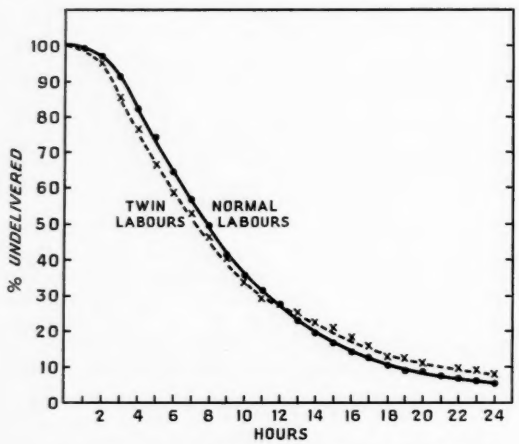

Fig. 3—To show that overdistension of the uterus, due to multiple pregnancy, does not prolong labour.

289 consecutive twin pregnancies occurred among 205 multigravidæ (1955–59) and 84 primigravidæ (1952–59). These are compared with 1569 consecutive " normal " labours in primigravidæ and multigravidæ, corrected to include 29% primigravidæ.

Estimation of Duration of Labour

Whatever arbitrary standard of time is taken for the purpose of classifying labour as prolonged, the assumption has to be made that an observer, or the patient, can assess accurately the duration of labour. It is possible to say to one or two minutes when the second and third stages finish; but can anyone determine the time of onset of the first stage? By our record systems and our teaching of midwives and doctors, we encourage the idea that parturition begins suddenly. The patient herself is bullied into declaring precisely when she first experienced symptoms of labour. For the sake of peace she states a time; but she knows, as we all know, that the onset is usually gradual with intermittent and indefinite warnings which may or may not be significant. Several hours or days may elapse before it is certain that parturition is in progress. All records and statistics dealing with length of labour are therefore to some extent fictitious.

The onset of labour was reckoned, in my series, by an overall assessment of several factors, such as the onset of pain, a " show ", dilatation of the cervix, the patient's general demeanour, or sometimes by guesswork and intuition. By any method mistakes are unavoidable but some can be corrected by retrospective analysis. How often is a woman regarded as being in false labour, and making an unnecessary fuss, only to prove later to have been in true labour for several days? More frequently mistakes are made in the opposite direction: uterine inertia is diagnosed when true labour has not started, and this results in unnecessary alarm and treatment. This explains why some writers say that true inertia is a common form of uterine inefficiency, while others think it rare as compared with incoordinate uterine action. It also partly explains why views on the value of oxytocin and on the danger of prolonged labour are at variance.

Inefficient Uterine Action

It is now generally accepted that inefficient uterine action in labour has three main forms—inertia, incoordinate action, and cervical dystocia. By the last is meant obstruction of labour by refusal of the *external* os to dilate, despite good action of the uterus above; this is rare. Clinically it can be extremely difficult to distinguish between incoordinate action and uterine inertia, and often it becomes a matter of individual opinion. Indeed, conceivably one type of behaviour may change into the other in the same uterus during the same labour. More important, however, is the overall frequency of serious uterine dysfunction of any type. During 1955 and 1956 there were 152 such cases among a total of 6830 deliveries (2·0%) at Mill Road Maternity Hospital. Experience there, confirmed by that of many others, indicates that serious uterine inefficiency complicates 1–2% of all labours, and 4% of first labours. It is this which is the chief cause of prolonged labour.

Dangers of Prolonged Labour

The main danger of prolonged labour in the past was puerperal sepsis. This is still common, and among the 1955–56 series the frequency of puerperal pyrexia was five times greater than for the hospital as a whole (32% compared with 6·2%). This occurred despite the free use of antibiotics prophylactically, and it tallies with the experience of Sturrock and Brown (1956). Yet none of our patients died or was seriously ill. Ascending uterine infection, which is inevitable with prolonged labour, is now more a threat to the fœtus than to the mother; not only does its amniotic sac and respiratory tract become infected, but even septicæmia may develop.

From the mother's standpoint, the chief danger today of prolonged labour is ketoacidosis. In the past this was usually called maternal exhaustion, and its clinical features were labelled " signs of maternal distress ". These include deeper and more rapid respiration, tachycardia, dehydration, and pyrexia. Ketoacidosis arises primarily because of the activity of uterine and other muscles during labour, but it is accentuated by starvation, vomiting, and loss of sleep. It can only be prevented by the liberal administration of glucose; and, bearing in mind that the patient may be vomiting, that her digestive system is disturbed, and that she may later require general anæsthesia, the glucose should always be given intravenously. Indeed, once labour has been in progress for twenty-four hours, and before then if four-hourly testing of the urine reveals acetone, there is a clear indication for infusing glucose intravenously (in water or saline) and for continuing to do so until delivery is completed. When clinical evidence of dehydration and ketoacidosis is already present, more than a slow infusion of 5% glucose is required. It takes 3 litres of fluid to counteract dehydration which is clinically obvious; and 1 litre of a 5% solution provides only 50 g. of glucose, which is quite inadequate when acetonuria is found. In such circumstances a stronger solution, running freely, is required initially.

One of the secondary effects of untreated ketoacidosis is the mobilisation of potassium from the tissues in an attempt to restore the acid-base equilibrium. This does not show by way of blood-potassium levels, but it probably explains the paralysis of certain involuntary muscles, such as those of the colon, which is a feature of prolonged labour. This as well as the ketosis may affect uterine action adversely, and it is therefore not surprising that a glucose infusion alone often appears to improve uterine efficiency.

The fœtus is at greater risk than the mother when labour is prolonged. It is threatened not only by amnionitis but also by the toxic effect of maternal ketoacidosis. Above all, however, the fœtus is liable to develop anoxia from a failing placental circulation. The circulation of the uterus and

placental bed is always reduced by labour contractions (Wright et al. 1958) and it is reduced even more when uterine action is strong and incoordinate (Johnson and Clayton 1955). Indeed, the fœtus can be killed within a few hours by hypertonic uterine action; this is true even when the membranes are unruptured.

The danger to the fœtus is less when prolonged labour is due to true inertia, because there is little uterine muscular activity to cause maternal ketoacidosis and to impede the placental circulation. It is increased, however, if prolonged labour is superimposed on other factors, such as elderly primigravidity, toxæmia, hypertension, or post-maturity, all of which tend to make the placenta relatively inefficient.

The Results of Prolonged Labour

Despite all these hazards, mere prolongation of labour need not be attended by the disastrous results which past experience suggests. In Mill Road Maternity Hospital, during 1948–57, there were 259 labours (0·8% of all deliveries) which lasted more than forty-eight hours. Among these (" booked " and " unbooked ") the uncorrected perinatal mortality-rate was 3·4%, as compared with the annual overall hospital perinatal rates of 3·8–5·3% during the same years. This at first suggests that women who are long in labour have the best chance of a live and healthy child. But one has to remember that a large proportion, perhaps 50%, of the overall perinatal mortality-rate is accounted for by prematurity, whereas few of the babies born after prolonged labour are premature. None of the mothers died or was seriously ill, although the protracted labour doubled the maternal morbidity-rate (10·7% and 20%). The incidence of postpartum hæmorrhage was less in prolonged labour (4·7% and 2·7%).

The overall maternal and fœtal morbidity-rates were better than might be expected, but was this conservative management of these patients justified by the method of ultimate delivery? The mode of delivery in the 259 labours which lasted longer than forty-eight hours was:

Spontaneous vaginal delivery	64	cases
Forceps delivery	108	,,
Cervicotomy and forceps delivery	14	,,
Assisted breech delivery	10	,,
Cæsarean section	63	,, (*24*%)

from which it will be seen that 76% resulted in vaginal delivery. 196 women escaped the cæsarean section which would have been their lot had a rigid time rule been applied.

These results were obtained only because women and babies exposed to long labour were carefully supervised, and because ketoacidosis was prevented by the liberal use of intravenous infusions of glucose. The patients were also carefully selected by the exclusion of most of those who were advanced in years, who had a history of infertility, who had hypertension or pre-eclampsia, and whose babies were postmature. Moreover, the figures do not show the very large number of women whose labours were terminated by cæsarean section for inefficient uterine action before the lapse of forty-eight hours. Thus, any sign of fœtal anoxia prompted immediate operation even though the labour had only been in progress for twelve or twenty-four hours. Cæsarean section was also often performed before forty-eight hours when it was clear that labour was arrested. Indeed, a conservative policy in regard to prolonged labour is justified only so long as mother and baby are kept in good condition, and provided that progress—as manifested by dilatation of the cervix and descent of the presenting part—is being made.

This matter of continued progress is more important than the clock. Once it is clear that labour is halted active intervention is nearly always indicated.

Prolonged Second Stage

This last principle is as important in the management of the second stage of labour as it is of the first. Here again, there is a traditional time limit for the second stage of two hours in a primigravida and one hour in a multigravida. Nevertheless, it is not many years since it was common for the second stage to be allowed to continue for six to twelve hours on the grounds that the uterus was inert.

The old fears of using forceps, and of delivering the baby in the presence of uterine inertia, have fortunately gone. But there is still reluctance to assist the delivery until the arbitrary time limits have expired, or unless the fœtus shows signs of anoxia. Yet what is to be gained by waiting, once it is clear that progress in the second stage is arrested? The mother suffers pain, and the vagina may, by continued distension, be damaged, with the ultimate results of cystocele or rectocele. More important, however, is that the fœtus is at far greater risk from anoxia in the second stage than in the first stage. Once the presenting part leaves the uterus, the placental site is subjected to uterine retraction as well as contraction, and its circulation is impaired sooner rather than later. And the placenta which is postmature, or which has been exposed to toxæmia, hypertension, or even a prolonged first stage, is more vulnerable.

Under present-day conditions, and provided local anæsthesia is used, far more babies are lost from delay in applying forceps than from using them too soon. It is safer to anticipate fœtal distress than to wait for signs to appear. Writing on this subject a few years ago (Jeffcoate 1953), I pointed out that the forceps-rate at the Liverpool Maternity Hospital had risen in twenty-five years from 7 to 17% for all cases. In 1958 it was about the same (17·6%). At Mill Road Maternity Hospital, where the proportion of multigravidæ is higher, the rate for 1958 was only 6·4%. For comparison, the forceps-rate at the National Maternity Hospital, Dublin, was 11·7% in 1958, and 11·2% in 1959. If these figures be accepted as a reasonable average for all cases, then primigravidæ whose deliveries are so often held up by mere inelasticity of the vagina (rather than perineum) require assistance with forceps in not less than 20% of cases. At the Liverpool Maternity Hospital during 1959 and 1960, 697 out of 2540 primigravidæ† (27%) were delivered with forceps. Without this assistance many would have lost their babies. And yet it is still argued that it is safe for many primigravidæ to be delivered at home. Among primigravidæ in England and Wales, who were carefully selected for their normality to have their babies at home during 1956, the stillbirth-rate was 20 per 1000—that is nearly as high as the rate for the whole country (Ring 1960).

The above figures represent a very conservative view of the need to apply forceps to shorten the second stage of labour. I recently analysed my personal management of 581 deliveries among women doctors and doctors' wives. 22% were completed with forceps, and the figure for primigravidæ was 39%. Of the 128 babies delivered with forceps none was stillborn but 2 died neonatally—1 from prematurity (weight 2 lb. 6 oz.) and 1 from anæmia resulting from rupture of vasa prævia. Moreover, at least 2 babies were lost because forceps were not used.

†Primigravidæ include those with previous abortions only, as well as those pregnant for the first time. The incidence of forceps delivery in the two groups was the same.

Oxytocin

Dr. C. F. V. Coyle comments, in his report on the work of the National Maternity Hospital, Dublin, for 1959, that one explanation of the fewer cases of prolonged labour, and of the improved fœtal salvage, is the freer use of oxytocin infusions. Some decry this great advance in treatment, failing to recognise any difference between this and the admittedly dangerous practice of giving divided doses of oxytocin intramuscularly. I have used oxytocin infusions regularly since 1947, and I have never seen harm result. The technique gives complete control of the uterus because the effect of oxytocin disappears immediately the tap is closed. Any hormone remaining in the blood-stream is destroyed or inactivated within a few minutes (Berde 1959). In cases of true uterine inertia the effect of this treatment is generally quite remarkable, but oxytocin infusion is not always the answer to prolonged labour.

Theobald et al. (1956) and Goldman (1959) suggest that failure may be due to delay in initiating treatment. It is certainly important to start treatment as soon as there is a

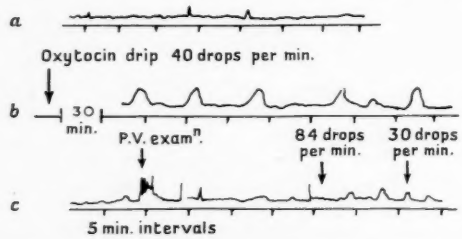

Fig. 4—A uterus becoming refractory to oxytocin.

(*a*) Tocograph of primigravida 12 hours after spontaneous rupture of the membranes, with little uterine activity.

(*b*) Uterine contractions were well established within 30 minutes of starting an intravenous infusion of oxytocin (5 units per litre).

(*c*) After 8 hours' continuous treatment with oxytocin the uterus no longer responded, even though the rate was increased to 84 drips per minute. The cervix was then only 2 fingers dilated. The patient was ultimately delivered by cæsarean section.

clear indication, and not to wait until labour has continued for thirty-six hours or more, and until the situation is prejudiced by maternal ketoacidosis. Even so, not more than 50–60% of cases show a good result attributable to the oxytocin. Failure occurs when the uterus is incoordinate rather than inert. This is probably because oxytocin does not change the quality of muscular activity; it merely accentuates that which is already present (Jeffcoate 1949, Jeffcoate et al. 1952). It may be that stimulation of the upper segment can sometimes overcome a minor degree of lower segment hypertonus. Nevertheless, when labour is complicated by severe incoordinate activity, oxytocin often makes matters worse, increasing the spasm wherever it may be found. This conclusion, based on clinical observations, is confirmed by Ingelman-Sundberg's (1958) demonstration that oxytocin causes contraction of the lower segment and cervix in certain types of abnormal uterine action.

It may be added that prolonged administration of oxytocin sometimes causes the uterus to become refractory to further doses of the same hormone (fig. 4).

Antispasmodics

When delay in the first stage of labour is caused by incoordinate uterine action, the object of treatment is to allay hypertonus and spasm. Unfortunately, except for

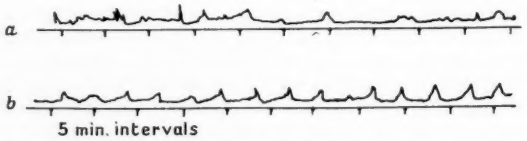

Fig. 5—External tocograph in a primigravida with incoordinate uterine action.

(*a*) Before treatment: 18 hours' labour, cervix three fingers dilated, contractions irregular in time and force.

(*b*) After 7 hours' treatment by continuous intravenous infusion of pethidine (total dose 400 mg.): the contractions were regular. Labour was completed by easy low forceps operation 3 hours later—i.e., after 28 hours' labour.

certain inhalation anæsthetics, there is no known drug which will quieten the normally labouring uterus although a possibility for the future is a preparation which will inactivate the naturally circulating oxytocin (Berde 1959). Meanwhile, there is some evidence that *abnormal* spasmodic action of the uterus can occasionally be improved by morphine and pethidine (Bickers 1942, Jeffcoate et al. 1952, Jeffcoate 1959). With this objective pethidine can be given by continuous intravenous infusion (300 mg. per litre). This technique is safe because the rate of infusion can be varied according to the sensitivity of the patient. During many years I have never seen harm come to either mother or child from this treatment, even though as much as 800 mg. has sometimes been given in twenty-four hours. In certain cases both pethidine and oxytocin are given, either simultaneously or alternatively, with apparent advantage.

Although pethidine sometimes seems to have a good effect (fig. 5), it is unreliable. When uterine activity returns, it may be as incoordinate as before (fig. 6). It is nevertheless the best of all antispasmodics so far tried.

Disproportion and Inefficient Uterine Action

In the past, prolonged labour often meant obstructed labour. Cases of grossly contracted pelvis, of transverse lie, and of hydrocephalus were overlooked or neglected. Under modern conditions these are recognised and treated early. There is therefore a tendency to regard prolonged

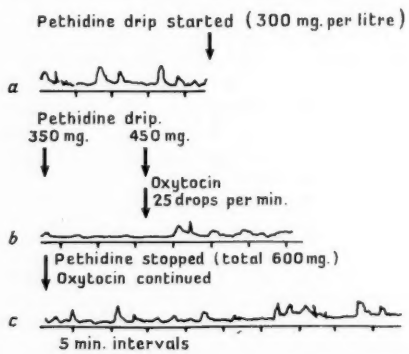

Fig. 6—Incoordinate uterine action treated unsuccessfully with pethidine.

(*a*) Primigravida 24 hours in labour, cervix two fingers dilated, contractions irregular in frequency and amplitude: treatment with pethidine infusion (300 mg. per litre) was then started.

(*b*) Tocograph after 350 mg. pethidine had been given intravenously: the abnormal contractions seemed to have been suppressed. After 450 mg. pethidine the contractions were restarted with an oxytocin infusion (5 units per litre).

(*c*) After 600 mg. pethidine the contractions returned but were irregular and incoordinate, and oxytocin did not alter them. The cervix did not dilate, and delivery was ultimately by cæsarean section.

labour as being generally the result of a primary disorder of uterine action. This is dangerous; for it is well established that, whereas the uterus of the multigravida generally reacts to mechanical difficulty by becoming more active, and ultimately by rupturing itself, that of the primigravida nearly always responds by inertia or incoordinate behaviour. The degree of disproportion necessary to cause uterine inefficiency need not be great and is easily disregarded.

So far as the second stage of labour is concerned, the part played by an inelastic vagina and perineum, and by faulty rotation of the fœtal head, in bringing about failure of uterine action has been recognised for centuries. The picture was previously described as one of secondary inertia, or of exhaustion of the uterus due to its efforts to overcome the obstacle to delivery. And clinical observation now goes to suggest that disadvantageous mechanical factors may be equally important in causing uterine inefficiency in the first stage of labour.

TABLE I—DURATION OF LABOUR RELATED TO MATERNAL HEIGHT

Patients	No. of cases	Average duration (hr.) of labour	50% delivered in (hr.)	75% delivered in (hr.)	Undelivered after 24 hr. (%)
Primigravidæ shorter than 5 ft. 1 in. ..	141	15·7	12·5	18·5	*16*
" Normal " primigravidæ	697	13·5	11·5	16·1	*8·9*
All primigravidæ ..	1110	14·2	12·2	..	*10·5*

Thus, even when cases of gross pelvic contraction are excluded, it can be shown that the overall duration of labour is related to maternal height which, in general, reflects pelvic capacity. During 1958–59, in Mill Road Maternity Hospital, 141 out of 1110 consecutive primigravidæ delivered vaginally (single births only), were less than 5 ft. 1 in. (1.53 m.) tall. Among these the average duration of labour was 15·7 hours, which compares with 14·2 hours for all primigravidæ delivered vaginally, and with 13·5 hours for " normal " primigravidæ (table I).

The size of the baby is equally important, and a direct relation between the length of labour in primigravidæ and the birthweight of the fœtus is shown in table II. Similarly it can be shown that any group of cases with inefficient uterine action contains a greater number of large babies than does a control series (table III). Although some women deliver large babies quickly and easily, prolonged labour (especially in primigravidæ) is often associated with undue fœtal size. It is therefore a good practical rule, when meeting a case of otherwise unexplained faulty uterine action and slow dilatation of the cervix in a primigravida, to consider whether the baby is a pound or so heavier than had previously been thought. This becomes even more important when the breech is presenting, because the fœtal mortality in such circumstances is mainly governed by fœtal size.

TABLE II—DURATION OF LABOUR IN PRIMIGRAVIDÆ RELATED TO WEIGHT OF BABY
(MILL ROAD MATERNITY HOSPITAL, 1958–59)

Weight of baby	No. of cases	Average duration (hr.) of labour	50% delivered in (hr.)	75% delivered in (hr.)	Undelivered after 24 hr. (%)
5 lb. 8 oz. (2500 g.) and under ..	89	9·8	10	14	*3·6*
5 lb. 9 oz–7 lb. 15 oz. (2501 g.–3628 g.)	557	13·1	11	15·5	*8·7*
8 lb. (3629 g.) and over	140	15·0	13	18·8	*11·4*
All " normal " primigravidæ	697	13·5	11·5	16·1	*8·9*

TABLE III—INEFFICIENT UTERINE ACTION IN PRIMIGRAVIDÆ RELATED TO FŒTAL BIRTH WEIGHT
(MILL ROAD MATERNITY HOSPITAL)

Weight of baby	1110 primigravidæ (1958–59)	227 cases of inefficient uterine (1953–56)
5 lb. 8 oz. (2500 g.) and under	8·5%	4%
5 lb. 9 oz.–7 lb. 15 oz. (2501 g.–3628 g.)	78·0%	66%
8 lb. (3629 g.) and over ..	13·5%	30%

Sometimes the mechanical problem associated with inefficient uterine action is due to an abnormal position of the presenting part. Thus, a posterior or transverse position of the occiput appears to influence uterine action adversely in certain cases. This at least is true of the second stage, when the cause-and-effect relationship is demonstrated by the fact that, if the fœtal head is rotated, either spontaneously or by the obstetrician, uterine behaviour thereafter improves. It is also substantiated by the observation that oxytocin therapy for uterine inertia associated with an occipitoposterior position does not cause the fœtal head to rotate (Jeffcoate et al. 1952).

A common observation is that inefficient uterine action is often seen in those cases in which the fœtal head remains high until the onset of labour. It remains high without apparent cause, and this is generally regarded as further evidence of an association between the uterine disorder and minor degrees of bony disproportion. In certain cases this may be correct, but in the majority another explanation is more acceptable. Descent of the fœtal head in the later weeks of pregnancy is normally determined by increasing dominance of the uterine fundus over the lower segment. Indeed, the fœtal head cannot engage unless the lower segment dilates. So, when the fœtal head remains high in the absence of disproportion, it probably means

TABLE IV—DURATION OF LABOUR IN PRIMIGRAVIDÆ RELATED TO MATURITY OF FŒTUS
(SINGLE BIRTHS AT MILL ROAD MATERNITY HOSPITAL, 1958–59)

Maturity	No. of cases	Average duration of labour (hr.)
" Mature " babies (weight more than 5 lb. 8 oz. [2500 g.], and born after less than 291 days' amenorrhœa)	697	13·5
" Postmature " babies (born after more than 291 days' amenorrhœa)	212	15·3
" Mature " babies (weighing 7 lb.–7 lb. 15 oz. [3175 g.–3628 g.])	281	13·6
" Postmature " babies (weighing 7lb.–7lb. 15oz. [3175 g.–3628 g.])	86	15·4

that the uterus is failing to demonstrate its normal polarity and that the lower segment is not forming. In other words, incoordination is present even before the onset of labour. It is therefore necessary to entertain the concept that faulty uterine action can occur in late pregnancy as well as during labour, and that one of its signs is a failure of the fœtal head to engage. When this happens it is not surprising that the subsequent labour is also complicated by incoordinate behaviour of the uterus.

Postmaturity and Inefficient Uterine Action

In 1952 Stewart reported an association between postmaturity and faulty uterine action. There certainly appears to be a type of case in which the onset of labour is delayed, the cervix is not taken up, and the presenting part remains high. Labour may threaten at the time expected, and then all symptoms subside and the pregnancy continues for two or three more weeks. When labour ultimately begins, it proceeds very unsatisfactorily.

That there is a relation between postmaturity and

TABLE V—DURATION OF LABOUR IN ELDERLY PRIMIGRAVIDÆ (AGED 35 AND OVER)

Patients	Average duration of labour (hr.)	50% delivered in (hr.)	% undelivered in 24 hr.
697 consecutive "normal" primigravidæ (1958–59)	13·5	11·5	*8·9*
1110 consecutive primigravidæ delivered vaginally (1958–59) ..	14·2	12·2	*10·5*
157 consecutive elderly primigravidæ delivered vaginally (1953–59)	17·2	13·5	*18·5*

inefficient uterine action is shown by table IV. It might be suggested that this depends merely on the fact that postmaturity results in a larger baby, but clearly postmaturity operates even when babies of similar birthweight are compared. Thus for babies weighing 7–8 lb. the average duration of labour differs by about two hours, according to whether they are mature or postmature. It therefore seems necessary to postulate that, in these cases, the failure of the patient to enter labour is again a manifestation of disordered uterine action present during late pregnancy and then continued into labour itself.

Parity and Inefficient Uterine Action

Faulty uterine action is essentially a disease of the primigravida (Jeffcoate 1949, Jeffcoate et al. 1952, Jeffcoate and Hibbard 1960), and when seen in the multigravida it nearly always takes the form of the less serious true inertia. Among 152 cases in Mill Road Maternity Hospital, in 1955–56, there were only 22 multigravidæ (14·5%). Most of these had hypotonic inertia, and one had cervical dystocia resulting from previous amputation of the cervix.

TABLE VI—INEFFICIENT UTERINE ACTION RELATED TO AGE (PRIMIGRAVIDÆ AND SINGLE BIRTHS ONLY)

Age (yr.)	1000 consecutive primigravidæ (1953–56)		227 cases of abnormal uterine action (1953–56)	
Less than 20	17%		12%	
20–24	51%	74%	46%	70%
25–29	23%		24%	
30–34	7%	8·5%	13%	18%
35–39	1%		4%	
40–44	0·5%		1%	

Among primigravidæ age also plays a part, both in determining the length of labour and inefficient uterine action. In table V is shown the duration of labour in primigravidæ aged more than 35, as compared with that for all primigravidæ and for "normal" primigravidæ. Advancing years raises the average length of labour by about four hours. Similarly, in any series of cases of abnormal uterine action the proportion of elderly primigravidæ is higher, and table VI shows that the chance of this disorder rises after the age of 30.

But, irrespective of her age, the woman who has inefficient uterine action in her first labour rarely experiences similar trouble in later deliveries. As in normal labour, the uterus behaves more efficiently with experience. This is shown by the subsequent history of women whose first labours were complicated by severe uterine dysfunction (table VII). From this it appears that, when the first labour was complicated by such uterine inefficiency as to necessitate cæsarean section, 30 out of 46 women who were allowed to enter labour again were delivered vaginally—often spontaneously. A difficult forceps delivery at the end of a prolonged first labour was nearly always followed by an easy natural birth the second time.

TABLE VII—OBSTETRIC HISTORY AFTER INEFFICIENT UTERINE ACTION

Mode of delivery in second pregnancy	Cæsarean section for I.U.A. in first labour		Forceps delivery for I.U.A. in first labour	
	1946–51 series*	1953–56 series	1946–51 series*	1953–56 series
Spontaneous delivery	8	10	38	54
Forceps delivery	9	3	5	7
Cæsarean section after trial labour	11†	5	2	2
Elective cæsarean section	24	3	3	..

*Reported by Jeffcoate et al. (1952).
†Inadequate trial of labour in 3 cases.

It therefore seems clear that, provided it is given a chance, the uterus shows a natural tendency to function better with each successive confinement. When cæsarean section is necessary in the first labour the outcome for the second is largely governed by the degree of dilatation of the cervix at the time of operation. If it is less than half dilated, another section may be necessary, although the cervix attains further dilatation. If, however, the cervix is half or more dilated at the time of section, it will probably reach full dilatation on the next reproductive occasion.

The fact that one delivery tends to cure a uterus permanently of its dysfunction is of the utmost importance in the practical management of patients, and also in reaching any conclusion as to the ætiology of inefficient uterine action in primigravidæ. It clearly rules out psychological and nervous factors as important causes. The woman who has once experienced incoordinate uterine action is far more fearful of her second than her first labour. Indeed, it is difficult not to conclude that when disproportion between the size of the presenting part and the pelvis is excluded, the cause of a prolonged first stage of labour is often an organic resistance to dilatation on the part of the lower uterine segment and cervix.

Indeed, inefficient uterine action is no more than an exaggeration of the normal behaviour of the primigravid uterus. Once the resistance is overcome by the first delivery, subsequent labours are easy. This theory also readily explains why advancing years, a large baby, and postmaturity are all factors in the ætiology of incoordinate uterine action. They all imply added resistance of the lower uterus to dilatation, or "disproportion" between the presenting part and soft-tissue birth canal.

Conclusion

The overall conclusion is that abnormal prolongation of either the first or second stages of labour often means mechanical obstruction of some type and of some degree, even though the cause may at first appear to be uterine inefficiency. In the second stage the mechanical difficulty is usually an inelastic vagina or a presenting part which is large or malrotated. In the first stage, the underlying problem is pelvic contraction, a large baby, or, most often, obstruction by the lower segment and cervix. This obstruction may suppress or disturb the expulsive force of the uterus, because dilatation of the cervix is the natural trigger to the physiological release of oxytocin by the hypothalamus-pituitary system. In contrast to other forms of mechanical obstruction, however, there is always hope that time and patience may bring about diminution of the resistance in the soft tissue of the birth canal. There is, nevertheless, a limit beyond which time and patience are dangerous treatments, especially as far as the baby is concerned.

In these days of high death and injury rates from traffic accidents, it still remains true that the most dangerous journey made by any individual is through the 4 inches of the birth canal. No-one can safely loiter in crossing a road.

Similarly no baby can safely loiter in the cervix and vagina. But speed on a pedestrian crossing can also be dangerous if it is reckless, precipitate, and thoughtless. The same rule applied to obstetrics means that, while patience is permissible under certain circumstances, carefully planned active treatment aimed to speed the baby's journey is, if carried out by the expert working under hospital conditions, far safer than allowing even the slightest unnecessary prolongation of labour.

For the collection and analysis of hospital statistics I am indebted to Dr. B. M. Hibbard and Dr. V. R. Tindall. The tables and figures are reproduced by courtesy of *Revista de Obstetricia y Ginecologia de Venezuela*.

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PREDNISONE-GLYCOSURIA TEST FOR PREDIABETES

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LONG-TERM studies have shown that apparently healthy women whose pregnancies are abnormal (large babies, stillbirths, &c.) often develop diabetes later (Jackson 1960). Such an early stage of this disease, at which levels of blood and urine sugar are still normal, has been aptly termed " prediabetes ". When later, though the patient is still clinically well, the standard oral glucose-tolerance test (G.T.T.) has become clearly abnormal, the condition is best described as " subclinical diabetes ". The term " latent diabetes " should denote a state in which there is little or no residual evidence of a previous " temporary diabetes ". Latent diabetics may at different times be found to have subclinical diabetes, or to have prediabetes.

Because prediabetes, though giving a normal G.T.T., may cause abnormal pregnancies, or be a sign of acromegaly and Cushing's syndrome, we need a test which will reveal it. A partial answer has been the cortisone-stressed G.T.T. (C.G.T.T.), introduced by Fajans and Conn (1954). They found that of 295 relatives of diabetics who had given a normal G.T.T., 25% gave an abnormal C.G.T.T. (Fajans and Conn 1959). The C.G.T.T. is a standard oral G.T.T., performed after giving two oral doses of 50 mg. cortisone (or 62·5 mg. in people weighing more than 160 lb.), eight and a half and two hours previously.

Thus, while a large dose of corticotrophin or corticosteroid will induce hyperglycæmia and glycosuria even in normal subjects, a suitably small dose will induce it only in susceptibles such as prediabetics. It seemed to us possible that this hyperglycæmic and glycosuric response to corticosteroids might be assessed without any oral glucose, which would be an advantage because it would then be independent of the glucose-absorption rate. Finding that this was so, we have used a " prednisone-glycosuria test " instead of the C.G.T.T., and this paper records results in a total of 102 subjects which suggest that it satisfactorily demonstrates prediabetes.

Subjects Tested

Normal subjects.—12 non-pregnant hospital inpatients, with non-endocrinological conditions—e.g., attempted suicide, awaiting minor surgery, &c.—from 20 to 58 years of age (mean =42); none had a family history of diabetes, or had given birth to an infant weighing more than 9 lb., and in none had glucose ever been detected in the urine. Results of an oral G.T.T. were normal; and in this test they did not have excessive glycosuria (i.e., renal glycosuria was absent; see appendix 2).

Normal pregnant group.—11 inpatients aged 20–43 years (mean=28), admitted for some trivial complication between the sixteenth and thirty-sixth week, fulfilling the criteria of normality listed above.

Possible latent diabetics.—13 patients with a history of previous glycosuria, sometimes also diagnosed as diabetic, but now without symptoms or signs of diabetes, and in whom the G.T.T. results were normal. Their ages ranged from 22 to 66 years (mean=38).

Relatives of diabetics.—There were 21 of these, with no clinical signs or symptoms of diabetes, all of whom were free from glycosuria, and with normal G.T.T. results. Their ages ranged from 16 to 49 (mean=31).

Mothers of babies weighing more than 9 lb.—These 13 women were collected from those attending the hospital obstetric department. Their ages were between 23 and 41 (mean=32) years. None had a diabetic relative; and none had had glycosuria. Results in this group are described in an accompanying paper (Davey et al. 1961).

Mild diabetics.—10 typical patients, aged 46–73 (mean=57) years, selected for the mildness of their disease as a suitable group for testing the design of the test.

Acromegalics.—Only those cases with a normal G.T.T. were tested. A total of 15 tests were done, on 8 acromegalics, whose ages were 31–61 years (mean=44). The patients were classified as either being in an " active " phase (5), " inactive " phase (3), or " possibly active " phase (7)—i.e., most cases were tested both before and also after implantation. Patients were considered to be " active " when they were completely untreated, or had had no significant response to external irradiation of the pituitary; " inactive " when clearly showing regression clinically after receiving 10,000–20,000 rads from pituitary implantation of radioactive seeds (Fraser and Joplin 1961), and " possibly active " when the observation period following pituitary implantation was too short for proper assessment.

Renal glycosurics.—Tests were also performed on a further group of 14 patients (12 of them pregnant) found to have glycosuria but a normal G.T.T.

The Test

Preliminaries

For three days the patient is given a diet containing 300 g. carbohydrate daily,† and urine collected before breakfast, lunch, and supper is tested with Benedict's

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† Though others, (e.g., Wilkerson et al. 1960) have recently suggested a different dietary intake for such tests, we believe there are better reasons for using this diet level.

reagent. This can be done in the outpatient department. A simplified oral G.T.T.‡ is then performed, for which blood is taken when fasting, and at one and a half and two and a half hours after giving 50 g. glucose; and a three-hour urine sample is collected. If these data reveal frank diabetes, the rest of the test is unnecessary. If renal glycosuria is disclosed (either by glycosuria when fasting with a normal fasting blood-sugar, or, in milder cases, by excessive glycosuria during a G.T.T. which gives a normal curve), the interpretation of the subsequent prednisone-glycosuria test will be difficult, but the test is still practicable.

Procedure

For the test, 20 mg. prednisone is given at midday, 4 P.M., and 8 P.M.; and the subject fasts from 7 P.M. until 6 A.M. next morning. Urine is collected from 10 P.M. to 6 A.M. for glucose estimation, the results being expressed in milligrammes of glucose per hour. Where possible, and especially with a known renal glycosuria, blood is also taken at midnight and 1 A.M.

We took blood by fingerprick directly into fluoride tubes; duplicates were usually obtained.

Urine was collected directly into containers with chlorhexidine ('Hibitane') 1/2000; this is more effective than the

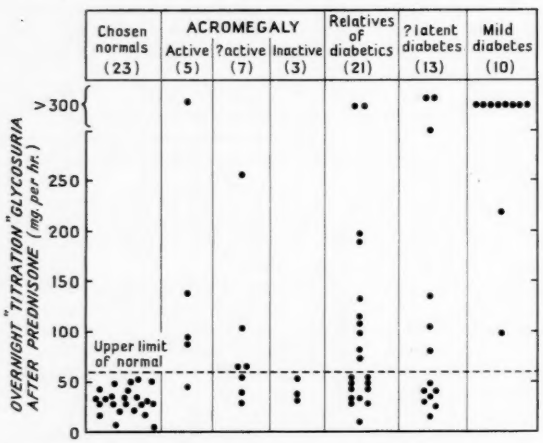

Fig. 1—Standard prednisone-glycosuria test for prediabetes: results in 75 patients. The upper limit of normal glycosuria is 60 mg. per hour of "titration" glucose.

Apart from the 10 diabetics all these patients had normal standard G.T.T. results. (Latent diabetics were tested because of past history of glycosuria or former diagnosis of diabetes, but they currently had normal G.T.T. results and no glycosuria.)

toluene we originally used, because it conserves the glucose content of infected urine at room temperature. We kept the urine in a refrigerator until sugar could be estimated by copper-thiosulphate titration (King and Wootton 1956). After an initial series of tests using the glucose-oxidase method of true urine sugar (Froesch and Renold 1956), the "titrated" glucose value was found to be sufficiently reliable for our test. (See appendix 1).

Blood-sugar was estimated mainly with the 'Technicon' autoanalyser, by the method of Hoffman (1937), but a few were done by Harding's modification of the Shaffer-Hartmann method (King and Wootton 1956). The two methods gave similar results. The standard errors of the principal methods based on duplicates obtained periodically through the study, were as follows: "titration" urine-sugar 4·4%; autoanalyser blood-sugars, when duplicate specimens were used, 3%.

‡ Throughout this paper we take a normal result of a glucose-tolerance test as one with the fasting and $2^1/_2$-hour capillary-blood-sugar values under 95 mg. per 100 ml., and the $1^1/_2$-hour value under 140.

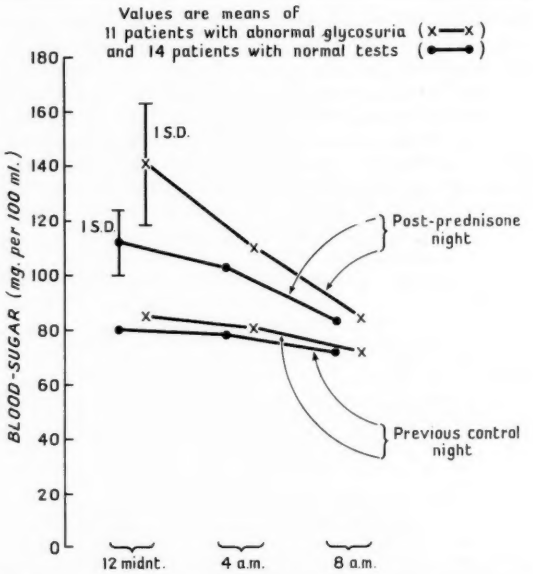

Fig. 2—Overnight blood-sugars during prednisone-glycosuria test, and on preceding control night.

20 mg. prednisone was given orally to 25 patients at midday, 4 P.M., and 8 P.M. "Titration" glucose excretion-rates were measured from 10 P.M. to 6 A.M. The patients were divided into two groups: 11 excreting >60 mg. per hr. (8 of these excreted <160 mg. per hr.), and 14 excreting <60 mg. per hr. Blood-sugar levels were measured at midnight, 4 A.M., and 8 A.M. on the control night and the prednisone night in each case. Mean overnight blood-sugar levels for the control night were similar in the two groups; but the group with abnormal results in the prednisone-glycosuria test had the higher values after prednisone.

Results

Normal subjects.—In both the pregnant and non-pregnant normal subjects, the value for "titrated" overnight urinary glucose after prednisone never exceeded 60 mg. per hour. In 23 such subjects tested, the mean value was 36 and the range (±2 S.D.) 12–58 mg. per hour.

Suspected prediabetics.—In 6 of the 13 possible latent diabetics, in 10 of the 21 relatives of diabetics, and in 9 of the 13 mothers of infants over 9 lb. in weight, "titrated" urinary-glucose levels after prednisone were above 60 mg. per hour (i.e., were abnormal) (fig. 1).

Mild diabetics.—In all 10 the levels were above 60 mg. per hour.

Acromegalics.—In 4 of the 5 "active" acromegalics the levels exceeded 60 mg. per hour. In the 3 "inactive" patients they were within normal limits.

Renal glycosurics.—After prednisone, abnormal overnight glycosuria was found in all 14 who were tested; the mean value was 825 mg. per hour, and the range 230 to 1800 mg. per hour.

Night Blood-sugar Estimations

In 14 subjects without glycosuria after prednisone the values for the midnight sample ranged between 90 and 133 mg. per 100 ml. (mean=111). In 11 patients (excluding the renal glycosurics) with glycosuria after prednisone, the values were higher (range=115 to 166; mean=141) (fig. 2). Samples at 1 A.M. gave very similar results to the midnight ones.

In all 7 renal glycosurics in whom night blood-sugars were tested the levels were within normal limits.

Discussion

The main corticosteroids, cortisol (hydrocortisone) and corticosterone, have a "glucocorticoid" action; and this is

a well-known adrenocorticol function (Britton 1930, Zucker 1949). Experimental evidence suggests that the corticosteroids impair peripheral glucose utilisation little if at all, and induce hyperglycæmia, and hence glycosuria, mainly by increasing the hepatic output of glucose. In studies on the normal subject cortisol has been found to produce glycosuria not only by raising the blood-sugar level but also by lowering the renal threshold, probably by increasing the glomerular filtration-rate (Froesch et al. 1958). The effect of medium dosage of cortisol, either orally or intravenously (200 mg. over eight hours), is maximal at four to eight hours, and recedes in about the same time (Froesch et al. 1958, West 1959). Perhaps it is partly because its hyperglycæmic action lasts longer that a cortisone-load test reveals prediabetes better than an oral dose of glucose.

The final pattern of the test was chosen after we had found that this dosage of prednisone induced no glycosuria in normals but substantial glycosuria in mild diabetics.

Further, at this time of the day the urinary true-glucose secretion is the lowest and most constant in normal subjects (appendix 2). On the other hand, this test seems reasonably sensitive to prediabetes, urine-glucose levels then being abnormal in about half (32) of the 62 tests on subjects chosen as likely to be prediabetic, even though in the preliminary observations their blood and urine sugars had all been normal.

We are accumulating further data on the sensitivity of the supplementary midnight blood-sugar index: of a total of 30 tests so far on subjects who have given abnormal glycosuric responses, 16 had abnormal midnight blood-sugar values. This blood-sugar supplement to the test offers useful confirmation of the urinary sugar results, and is an additional guard against interpreting " simple " renal glycosuria as prediabetes. Clearly, abnormal responses on the test can be more readily determined from the glycosuria in a whole-night sample than from a single midnight blood-sugar; but more than half of the abnormal test results would be detected by both.

In renal glycosurics, who will be picked up during the preliminaries, any type of cortisone-load test for prediabetes is difficult to interpret, since any increase of their hepatic-glucose output will produce less hyperglycæmia and more glycosuria than would be expected if the renal threshold were normal. Hence our finding of normal blood-sugar levels in renal glycosurics after prednisone may not exclude prediabetes. It may later become possible to allow for the lowered renal threshold by measuring the glycosuria by a glucose-tolerance test, and so to say whether the urine and blood sugars after prednisone suggest concomitant prediabetes and renal glycosuria. Meanwhile we could regard obvious renal glycosuria in non-pregnant subjects as itself suggestive of a prediabetic state (Miller et al. 1944, Ackerman et al.1958).

Several workers (Jackson and Woolf 1957, Carrington et al. 1958) have noted that, in glucose-tolerance tests, minor abnormalities are found more often in the groups likely to include future diabetics—such as relatives of diabetics, or mothers of large babies. These tests may disclose the first signs of subclinical diabetes; but if attention is to be paid to minor abnormalities, glucose-tolerance tests demand very careful clinical assessment, as well as meticulous supervision, blood-sugar estimations, and dietary and other preparation of the patient, &c., because many causes may give rise to slightly abnormal G.T.T.s and so to false positives. It is probably safer to regard minor or doubtfully abnormal results in the G.T.T. merely as indications for more sensitive tests such as the cortisone-load test, and a two-and-a-half-hour blood-sugar value clearly above the fasting level as definitely diabetic. Since by our definition the G.T.T. is normal in prediabetes, it can reveal only subclinical diabetes.

TABLE I—COMPARISON OF ABNORMAL RESPONSES IN THE CONN TEST AND PREDNISONE-GLYCOSURIA TEST

Series	Healthy relatives of diabetics with a normal standard G.T.T.		Normal subjects with a normal standard G.T.T.	
	No. tested	No. abnormal	No. tested	No. abnormal
I *Conn test*				
Fajans and Conn (1959)	295	75 (*25%*)	104	3 (*3%*)
Bertrand and Gilbert (1960)*	46	23 (*50%*)	59	21 (*34%*)
Goto et al. (1960)* ..	17	6 (*35*)%	9	0 (*0%*)
West (1960)	26	5 (*19%*)	44	8 (*18%*)
II *Prednisone-glycosuria test*				
Present series	21	10 (*48%*)	23	0 (*0%*)

* The standard oral G.T.T. was not recorded in this series.

Probably the most reliable method of detecting impaired glucose tolerance is the intravenous G.T.T. Duncan (1956a) found it not only consistently reproducible but also useful, after the sensitivity was increased with cortisone, in picking out prediabetics (1956b). When 200 mg. cortisone was given two hours before the intravenous glucose, 9 out of 19 " suspected prediabetics " responded abnormally, whereas in 20 normal subjects no effect was evident. Unfortunately, this intravenous technique is rather exacting, and unsuitable as a routine test. The promising results reported by Berger (1952), who used corticotrophin to make the oral G.T.T. more sensitive, have yet to be confirmed. He found that in all 14 relatives of diabetics the test results were " abnormal ", compared with 2 out of 24 normal subjects; but he performed no control G.T.T.

Other workers encountered difficulty in reproducing Conn's results with the cortisone-stressed oral G.T.T., possibly because of the variable results of the oral G.T.T. (table I).

West (1960), who tested subjects in whom potential diabetes was almost certainly present since their parents were both diabetic, obtained a similar incidence of abnormal test results in a group of normal subjects. German (1958) performed the Conn test on 80 subjects, half of whom were obese and half not. The two-hour blood-sugar level was similar in the two groups. He noted the inconsistencies of the oral G.T.T. in the 80 cases: though the mean rise in two-hour blood-sugar level in the C.G.T.T., compared with the control G.T.T., was 20 mg. per 100 ml., in 19 cases it fell. With a similar type of steroid-stressed oral G.T.T., Bertrand and Gilbert (1960) found the response of a group of 60 mothers of large infants differed from that of a group of 45 mothers of normal-sized infants; but when these 105 women were divided into a group of 46 with diabetic relatives, and one of 59 without, no significant difference in results was seen. Jackson (1960) also found that the Conn-type test often failed to pick out prediabetics in groups of subjects whose family history indicated that they almost certainly were potential diabetics.

The six-year follow-up by Fajans and Conn (1959), however, is impressive: among 191 relatives of diabetics, diabetes developed in 6 out of 34 with abnormal test results, but in only 1 of 57 with a normal result.

Theoretical advantages for our prednisone-glycosuria test over the Conn test are: (1) the corticosteroid dosage applies a larger stress for a longer time, and (2) the basic measure of the overnight glycosuria, possibly since it is a basal measurement, is less variable than the glucose-

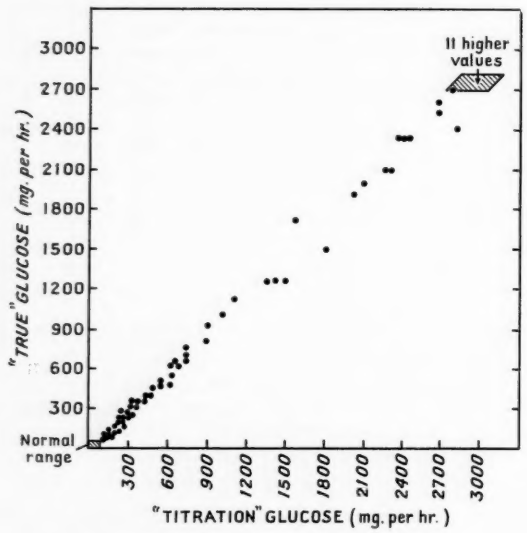

Fig. 3—Relation of " true "/" titration " glucose.

Points represent the " true " and " titrated " glucose-excretion rate (mg. per hr.) in 65 urine collections (from 22 patients) with values above the normal range.

tolerance test, as seen among normal subjects. But probably neither the Conn test nor ours will detect all prediabetics, though ours has always given normal results in normal subjects. Further, our test shows as many abnormalities among diabetic relatives as does the Conn test (table I).

Summary

The prednisone-glycosuria test—an alternative corticosteroid-load test for revealing prediabetes—is described. After three days of controlled diet, and simple preliminary blood and urine glucose estimations, three doses of 20 mg. prednisone are given at midday, 4 P.M., and 8 P.M., and urine passed between 10 P.M. and 6 A.M. is collected from the fasting subject. The overnight urinary-glucose output is measured by a simple titration method; over 60 mg. per hour is abnormal.

Where possible, blood is also taken at midnight and 1 A.M. for sugar estimation; over 133 mg. per 100 ml. is probably abnormal.

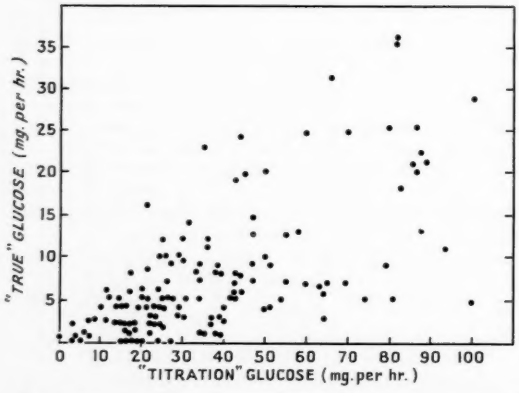

Fig. 4—Relation of "true"/"titration" glucose in normal subjects.

Inset: 139 urine collections from 19 normal people whose diet and activity were unrestricted.

All the 23 normal subjects tested had an overnight urinary glucose of less than 60 mg. per hour after prednisone. Among other subjects with normal results of glucose-tolerance tests and without renal glycosuria, abnormal results were found in 10 out of 21 relatives of diabetic patients, 9 out of 13 mothers with large babies, and 4 out of 5 active acromegalics.

14 subjects with renal glycosuria were also tested; but further studies are needed before the test-results in this condition can be fully interpreted.

We thank the following technicians for performing all the urinary-glucose analyses, and some of the blood-sugar estimations: Mrs. H. J. Bloch, Mrs. K. Vartan, and Mrs. B. Coates. We are also grateful to Dr. R. Haslam for estimating many blood-sugar levels on the 'Technicon' autoanalyser; and to our colleagues in the department of obstetrics and gynæcology for referring cases. We are indebted to the British Insulin Manufacturers for a grant.

Appendix

PRELIMINARY STUDIES TO DEFINE THE FORM OF THE TEST

(1) *Relation of urinary " true " glucose to " titrated " glucose values.*—Fig. 3 shows the correlation between these values in 204 urine samples, where both estimations were made. For the low quantity found in normal urine (0–35 mg. true glucose per hour), there is no significant correlation, but in all higher concentrations the correlation is very close. Since all the significant rises in urine-sugar in the prednisone-glycosuria test are into these higher ranges, the " titrated " glucose estimation is sufficiently specific.

(2) *Normal diurnal variation in urinary " true " and " titrated " glucose excretion and values during a G.T.T.*—The range of 24-hour urinary " true " glucose was found from estimations in 19 normal subjects to be 8–280 mg. (mean = 96). Overnight collections not only contain less glucose than daytime ones, but also show less variation (table II). For this reason, overnight collections for the prednisone-glycosuria test were adopted. From these values obtained during a normal G.T.T., we have defined the upper normal limit as 100 mg. per hour of "titration" glucose, levels beyond which imply renal glycosuria.

TABLE II—" TRUE " AND " TITRATED " URINARY-GLUCOSE (mg. per hr.) AT DIFFERENT TIMES IN NORMAL SUBJECTS

—	9 A.M.–9 P.M. (Free meals)		9 P.M.–9 A.M. (Starved)		9 A.M.–Midday (During G.T.T.)	
	" True " glucose	" Titration " glucose	" True " glucose	" Titration " glucose	" True " glucose	" Titration " glucose
Range . .	0–18	6–63	0–9	10–50	0–76	4–83
Mean . .	5	33	3	24	11	27
No. of subjects	19	19	15	15	15	15

Note least variation and lowest values overnight.

(3) *Inadequate glycosuric effect of smaller corticosteroid dose.*—Initially we tried cortisone in a dose of 25 mg. at the same times as is described for the standard test, namely at noon, 4 P.M. and 8 P.M. 4 normal subjects and 3 mild diabetics were tested, using the " true " urinary glucose method. In no instance was a rise found in the overnight glycosuria.

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PREDIABETES IN MOTHERS OF LARGE INFANTS

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WOMEN who will later develop diabetes mellitus often have abnormally large infants. The perinatal mortality among their children is high (Skipper 1933, Allen 1939, Miller 1946, Moss and Mulholland 1951, Pedowitz and Shlevin 1952, Jackson 1952, Hagbard 1958). It appears that the shorter the interval between pregnancy and the onset of diabetes, the greater is the incidence of large babies and the greater is the perinatal mortality. The perinatal mortality is thus about 30% for the five years preceding the appearance of overt diabetes (Miller et al. 1944, Moss and Mulholland 1951, Jackson 1952) and rises to about 37% in the two years immediately preceding the clinical onset of the disease (Hagbard 1958). The perinatal mortality in infants of "prediabetic" women may, in fact, be greater than in those of women with well-controlled frank diabetes. Parkin (1958), for instance, reported an overall perinatal mortality of about 21% in infants of overtly diabetic women.

In some women who have had an abnormally large child or whose infant was stillborn, or died neonatally, an oral glucose-tolerance test (G.T.T.) performed in a subsequent pregnancy is found to be of the diabetic type (Moss and Mulholland 1951, Jackson 1952, Lund and Weese 1953, Carrington et al. 1958, Wilkerson 1959). In most cases the G.T.T. reverts to normal in the puerperium (Lund and Weese 1953, Carrington et al. 1958, Wilkerson 1959); Jackson and Woolf (1957) followed up 10 women in whom the G.T.T. result was abnormal during pregnancy but reverted to normal in the puerperium, and found that they all developed clinical diabetes within three years. By no means all women whose infants are large, stillborn, or die neonatally, however, have abnormal G.T.T. results. Hagbard (1958) found abnormal G.T.T.s in 19·6%, Carrington et al. (1958) in 14%, and Wilkerson (1959) in only 10·7% of these women.

If erythroblastosis fœtalis is excluded, enlargement of the islets of Langerhans is typically found in infants whose mothers will develop diabetes, or are already diabetic (van Beek 1956). Jackson and Woolf (1958) performed G.T.T.s during the pregnancies of 12 women whose children were stillborn and were noted to have enlarged islets. They found that only 5 of the women had abnormal tests although 5 of the 7 with completely normal tests subsequently developed clinical diabetes.

It thus seems that in many women the G.T.T. will fail to detect a tendency to diabetes; it was because of the need for a test for detecting impairment of the reserve capacity of the pancreatic islets that Fajans and Conn (1954) introduced their cortisone-stressed G.T.T. More recently Joplin et al. (1961) have evolved an alternative test based on the measurement of the overnight glycosuria after administering 60 mg. of prednisone.

The preliminary results of prednisone-glycosuria tests, performed on (1) a group of 11 normal pregnant women and (2) on a group of 13 women who gave birth to large infants, are described and compared with those from (3) a group of men and normal non-pregnant women.

Methods

The prednisone-glycosuria tests were performed as described by Joplin et al. (1961), using the "titration" urine-sugar method. The blood-sugars were estimated in duplicate on a 'Technicon' autoanalyser, by a modification of the method of Hoffman (1937), which in our laboratory gives results closely approximating to the "true glucose" values obtained by a glucose-oxidase method.

The normal men and non-pregnant women, and the normal pregnant women were inpatients who denied having any family history of diabetes, whose G.T.T.s † were normal, and who were considered to have a normal carbohydrate metabolism. The normal pregnant women had been admitted for some purely obstetrical condition; their ages were 20–43 years (mean=28), and the duration of pregnancy at the time of testing varied from sixteen to thirty-six weeks.

The mothers of large infants had no apparent medical or obstetrical abnormalities. Some were tested between three and twelve months after delivery, and others early in a subsequent pregnancy (before twenty weeks). All had normal G.T.T.s, and denied any family history of diabetes.

Results

The overnight excretion of "titration" glucose after prednisone in individuals in the three groups is shown in fig. 1. The mean excretion-rate in the 10 normal patients was 28.0±11.7 mg. per hr., and in the 11 normal pregnant women 35·2±11·5. There was no significant difference between the two normal groups, and the combined mean excretion-rate of these two groups was 31·8±11·9 mg. per hr. If we take 60 mg. per hr. as the upper limit of normal, the probability of this level being exceeded by chance is less than 1 in 100.

Sixteen prednisone-glycosuria tests were performed on 13 mothers of large infants; in nine instances (representing 9 separate patients) the overnight excretion of "titration" glucose after prednisone was abnormally high.

The changes in the excretion-rate of urinary glucose produced by prednisone in the individual patients are shown in fig. 2. In 6 of the 11 normal pregnant women the rate decreased, whereas in all 10 of the men and normal non-pregnant women it increased slightly. The mean excretion-rate of the two groups, however, did not differ significantly.

Those patients who were classified as abnormal on the basis of the absolute rate of glycosuria after prednisone, also showed an abnormal increase in the rate of glycosuria as the result of receiving prednisone. The statistical pre-

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† We took as a normal standard result of the oral 50-g. glucose-tolerance test a fasting and a 1½-hr. blood-sugar of less than 140 mg. per 100 ml., and a 2½-hr. blood-sugar of less than 95 mg. per 100 ml., together with a glycosuria of less than 100 mg. of "titration" glucose per hour in the concurrent 3-hr. collection of urine.

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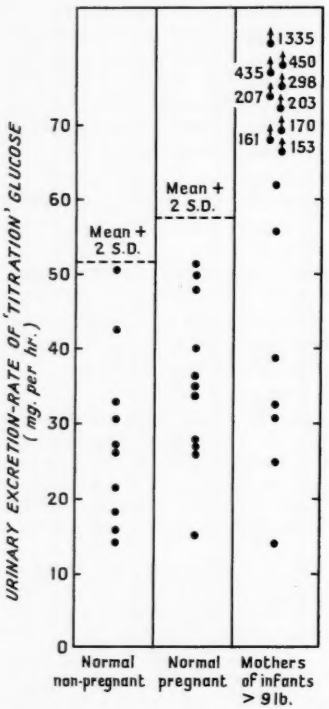

Fig. 1—Absolute excretion-rate of overnight urinary glucose after giving prednisone in 10 normal non-pregnant subjects, 11 normal pregnant women, and 13 mothers of large infants.

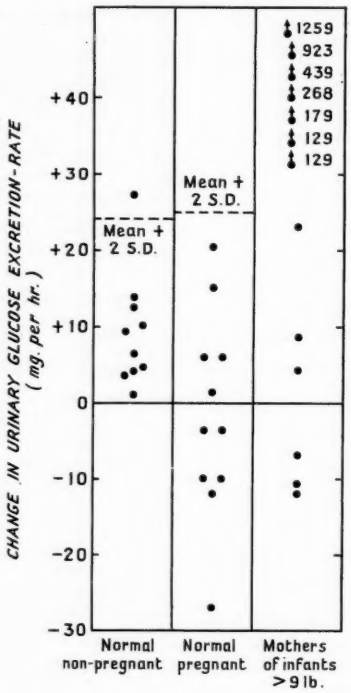

Fig. 2—Effect of prednisone on excretion-rate of overnight urinary glucose in 10 normal non-pregnant subjects, 11 normal pregnant women, and 13 mothers of large infants.

cision of the test using the absolute rate of glucose excretion was, if anything, greater than when the increase in rate after prednisone was used, and no advantage is gained by determining the latter.

Discussion

Women in whom the G.T.T. during pregnancy is abnormal, but who have no signs or symptoms of diabetes, have been designated " prediabetic ", but it would probably be more correct to regard them as having subclinical diabetes. van Beek (1956) suggested that if the G.T.T. reverts to normal in the puerperium the women should be described as " latent diabetics ", and Jackson (1959) used the term " temporary diabetes " for the period when the G.T.T. is abnormal. We propose, like Joplin et al. (1961), to reserve the term " prediabetic " for patients with a normal G.T.T. but an abnormal prednisone-glycosuria or other special test for impairment of the reserve capacity of the pancreatic islets. The fact that all the women who responded abnormally to prednisone in the present series had completely normal G.T.T.s supports the suggestion that the prednisone-glycosuria test is more sensitive than the standard oral G.T.T. in detecting a tendency to diabetes.

The abnormal responses to prednisone found in some mothers of large infants are similar to those found by Joplin et al. (1961) in other groups of patients suspected clinically of being prediabetic. It is reasonable to suppose that patients who have an abnormal prednisone-glycosuria test have some impairment of pancreatic function which, if it progresses, will result in overt diabetes. Women with abnormal prednisone-glycosuria tests may thus provisionally be regarded as prediabetic. It will be necessary, however, to follow-up for many years a number of women in whom prednisone-glycosuria tests are abnormal in order to establish that diabetes does in fact develop. It will also be important to study their obstetrical careers. If the prednisone-glycosuria test is a valid test of a tendency to diabetes, then women who respond abnormally should, in the absence of treatment, give birth to an abnormally large number of overweight infants, and the infants should have an abnormally high perinatal mortality.

The distinction between prediabetes, latent diabetes, and subclinical diabetes may be very important in pregnancy, as each grade may require different management and may carry a different prognosis for both mother and fœtus.

Carrington et al. (1958) treated 46 pregnant women with subclinical diabetes by carbohydrate restriction. Some were also given insulin; and in some labour was induced prematurely. There was only 1 neonatal death in this series, giving a perinatal mortality of 2·1%, as compared with 25·6% in their untreated control-series. Wilkerson (1959) treated a series of pregnant women in whom the G.T.T. was abnormal, with insulin " in the amount necessary to maintain normal glycæmia throughout pregnancy ". Some had a family history of diabetes; others had previously given birth to large babies or had had two or more pregnancies in which the infant was still-born, died neonatally or was congenitally abnormal. Wilkerson found that the incidence of large infants (9 lb. or more) in the patients treated with insulin was about 5%, as compared with 13% in an untreated series; and the perinatal mortality among infants of those treated was about 3%, as against 6% among the untreated.

This work suggests that carbohydrate restriction and/or insulin therapy, together with induction of premature labour, can significantly reduce the perinatal mortality in infants of women with subclinical diabetes. The place of these measures in the management of pregnancy in the prediabetic and latent diabetic women has yet to be evaluated.

If it is shown that the infants of women who have an abnormal prednisone-glycosuria test have an increased perinatal mortality, and that carbohydrate restriction, insulin, or induction of premature labour significantly reduce this mortality, then a test for prediabetes, such as the present one, may well have an important place in obstetrics.

Summary

The prednisone-glycosuria test was performed on 10 men and normal non-pregnant women, on 11 normal pregnant women, and on 13 mothers of large infants over 9 lb. In all of them, the glucose-tolerance test gave normal results. The rate of urinary excretion of glucose after prednisone in the normal pregnant women did not differ significantly from that in the normal men and non-pregnant women.

Taking the upper limit of normal for the rate of overnight glycosuria after prednisone as 60 mg. of " titration "

glucose per hour, 9 of the 13 mothers of large infants responded abnormally to prednisone.

Provided their renal threshold is not abnormally low, women with an abnormal glycosuria after prednisone should be regarded provisionally as prediabetic.

We are greatly indebted to Sister I. Shilton and to the nursing staff of the obstetric and medical wards of Hammersmith Hospital for helping with the tests, also to Mrs. B. Coates and Mr. A. Ayrton for the urine-sugar estimations, and to Dr. R. Haslam of the department of chemical pathology for the blood-sugar estimations.

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ACCESSORY ADRENOCORTICAL FUNCTION AFTER ADRENALECTOMY IN PATIENTS WITH BREAST CANCER

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BILATERAL adrenalectomy and oophorectomy may induce remarkable improvement in the course of metastatic breast cancer in women. In the few patients who gain worthwhile palliation, tumour deposits in the skin, lymph-nodes, viscera, and bones may regress for several years, with return of strength and wellbeing. Unfortunately, sooner or later renewed growth and multiplication of the tumour cells leads to relapse and death.

The mechanism of the response to adrenalectomy and oophorectomy is obscure, although it is reasonable to assume that endocrine surgery deprives the tumour cells of a hormonal factor essential for active growth. In the same way, eventual relapse may be due to the development of an accessory source of adrenal-ovarian hormones, which restore optimum conditions for tumour proliferation. Accessory adrenocortical tissue is known to exist in man (Graham 1953, Falls 1955).

The following investigations were conducted to determine whether there was evidence of returned adrenal function in patients with breast cancer treated by adrenalectomy and oophorectomy, who relapsed after initial regression.

Methods

Observations to detect residual adrenocorticol function were made in six patients whose metastatic breast cancer had regressed after bilateral adrenalectomy and oophorectomy. In four patients the tests were performed twice—firstly while the cancer was in remission, and later during relapse. In the other two women, whose cancer regressed after adrenalectomy, tests were performed only during relapse.

Tests to detect accessory adrenal function were made in hospital under strict supervision. They comprised serial estimations of adrenal hormones and their metabolites in the urine and peripheral blood before, during, and after a period when cortisone maintenance therapy (75 mg. per day) was stopped. This period varied from patient to patient, depending on the appearance of symptoms of cortisone lack (anorexia, nausea, vomiting, weakness, and hypotension), which necessitated restarting maintenance therapy. Throughout the whole period of study (which usually lasted about 12 days) all urine was collected, and the daily output of total neutral 17-ketosteroids was estimated by the method advised by the Clinical Endocrinological Committee of the Medical Research Council (1951). The urine was then pooled in 48-hour or 72-hour collections, and aliquots were used for estimating 17-ketosteroid fractions (Hobkirk 1958), œstrogens (Brown 1955, Brown et al. 1957), and pregnanediol (Klopper et al. 1955).

On the 3rd day of cortisone withdrawal, peripheral blood

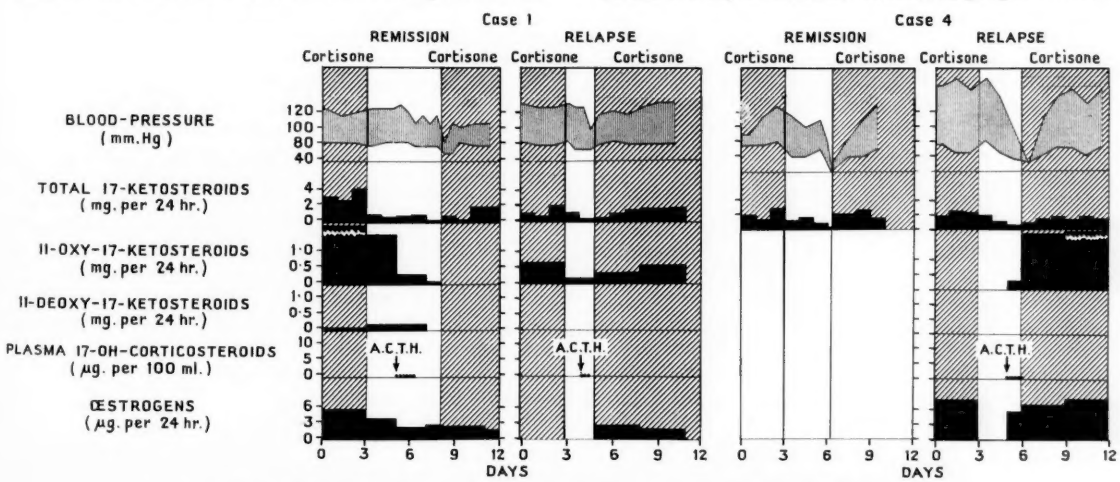

Fig. 1—Cortisone-withdrawal tests during remission and relapse in cases 1 and 4.
Cortisone 75 mg. per day was given over the periods indicated by shading; it was withdrawn on the 3rd day.

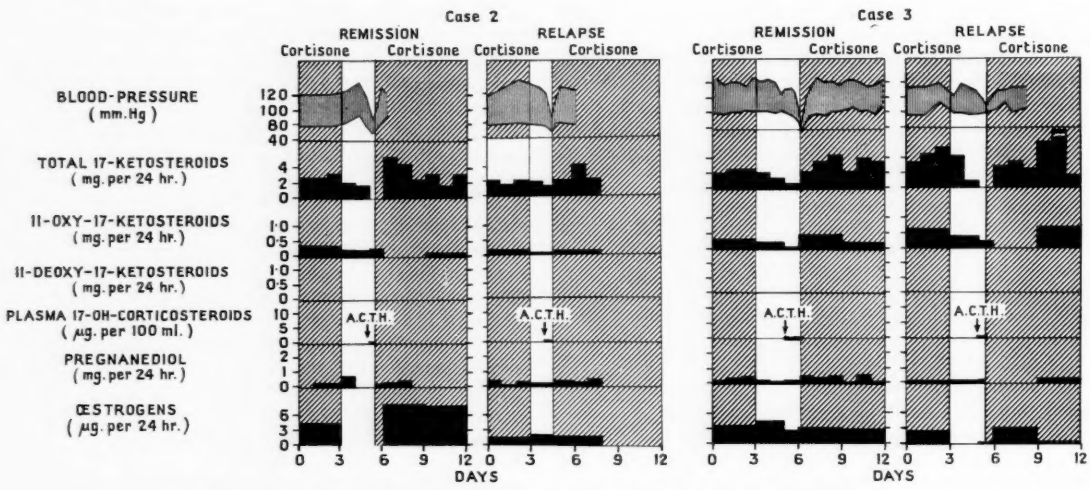

Fig. 2—Cortisone-withdrawal tests during remission and relapse in cases 2 and 3.

samples were taken before, and at 2-hourly intervals after, the intravenous infusion of corticotrophin (A.C.T.H.) 25 units in 200 ml. of 0·9% saline. The blood was immediately centrifuged, and the concentration of free 17-hydroxycorticosteroids in the plasma was estimated by a modification of the Porter-Silber reaction (1950), by Dr. V. J. O'Donnell, of the department of pathology, Glasgow Royal Infirmary.

Total 17-ketosteroids, 17-ketosteroid fractions, and pregnanediol are expressed in milligrammes per 24 hours, œstrogens in microgrammes per 24 hours, and plasma 17-hydroxycorticosteroids in microgrammes per 100 ml. plasma.

Results

The results of the hormone estimations during the tests in individual patients are shown in figs. 1–3 and table I.

In general the clinical effects of stopping cortisone were not apparent for 37–72 hours. Then the patient complained of nausea, loss of appetite, headache, muscle pains, and fatigue, and usually vomited. About 24 hours after the onset of these symptoms the blood-pressure began to fall, and then cortisone was restarted, usually by intravenous injection.

The time each patient was able to tolerate cortisone lack is shown in table II. This period was no longer when there was recrudescence of tumour growth.

The pattern of steroid excretion after cortisone withdrawal was similar in all patients, irrespective of the clinical behaviour of their cancer. When cortisone maintenance was stopped, the excretion of total 17-ketosteroids and 11-oxy-17-ketosteroids in the urine fell progressively, reaching zero or near-zero levels by the end of the withdrawal period. The absolute amounts of these steroids in the final pools of urine during the period of cortisone lack were dependent on the time of collection. In three patients in whom special collections of urine were made during the last few hours of cortisone withdrawal, 11-oxy-17-ketosteroids were absent from the urine. No noticeable difference in the excretion pattern of total 17-ketosteroids and 11-oxy-17-ketosteroids was associated with relapse of cancer.

The 11-deoxy-17-ketosteroid fraction was absent from the urine of all but one patient at all stages of the tests, both in patients with cancer in remission, and in those in relapse. In the exceptional patient (fig. 3, case 6) the amounts of these steroids were at the lower limits of the sensitivity of the method (ætiocholanolone 0·1 mg. per 24 hr.; androsterone 0·1 mg. per 24 hr.; β fraction 0·1 mg. per 24 hr.), which, taken in conjunction with the other findings, is probably of no significance.

In none of the patients were 17-hydroxycorticosteroids detected in the peripheral blood-plasma on the 3rd day of cortisone withdrawal, either before or after corticotrophin stimulation. In fig. 4 a typical test in one patient is compared with another repeated while maintenance cortisone was given, when the peripheral blood contained significant amounts of 17-hydroxycorticosteroids.

Small and quantitatively insignificant amounts of pregnanediol were detected in the urine of the four patients in whom it was estimated. The amount was influenced neither by cortisone withdrawal nor by the clinical behaviour of the cancer.

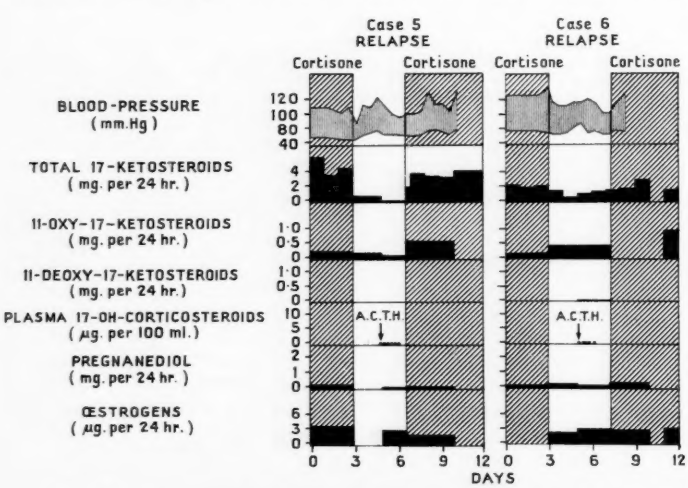

Fig. 3—Cortisone-withdrawal tests during relapse in cases 5 and 6.

TABLE I—DETAILS OF PATIENTS STUDIED

Case no.	1	2	3	4	5	6
Age at adrenalectomy (yr.)	51	30	49	65	46	37
Date of adrenalectomy	June 6, 1956	Sept. 24, 1957	July 23, 1957	April 26 1956	Nov. 14, 1957	July 10, 1956
Cortisone-withdrawal test in remission	May, 1957	April, 1958	May, 1958	May 1956,	...	..
End of remission	November, 1957	September, 1958	November, 1958	March, 1957	June, 1958	January, 1958
Cortisone-withdrawal test in relapse	December, 1957	February, 1959	April, 1959	April, 1957	August, 1958	June, 1958
Date of death	Dec. 17, 1957	May 25, 1959	Nov. 30, 1959	May 8, 1957	April 5, 1959	Oct. 1, 1958

Significant amounts of œstriol, œstrone, and œstradiol-17β were often found in the urine, but again the amounts did not vary with changes in cortisone dosage or with the patient's clinical response to adrenalectomy.

Pituitary implantation with yttrium-90 was subsequently performed when the response to adrenalectomy had run its course. No patient had further benefit from this procedure. In two cases postmortem examinations were performed, and no accessory adrenocorticol tissue was found.

Discussion

The detectable steroid hormones of adrenocortical origin in blood and their metabolites in urine are shown diagrammatically in fig. 5. In our observations, chemical methods were used to estimate total neutral 17-ketosteroids, 11-oxy-17-ketosteroids (11-hydroxyætiocholanolone, 11-hydroxyandrosterone, 11-ketoætiocholanolone, 11-ketoandrosterone), 11-deoxy-17-ketosteroids (ætiocholanolone, androsterone, dehydroepiandrosterone), œstrogens (œstriol, œstrone, œstradiol-17β), and pregnanediol in the urine, and 17-hyroxycorticosteroids (cortisol, cortisone) in the peripheral blood. In the totally adrenalectomised and oophorectomised woman, those steroids which are secreted selectively by adrenocortical and ovarian tissue should be absent.

Since the cortisone given as maintenance therapy will be detected in the peripheral blood by the Porter-Silber reaction, and will be metabolised to 11-oxy-17-ketosteroids in the urine, an accurate assessment of residual adrenocortical function after adrenalectomy can be made only when the intake of cortisone is stopped. Under these circumstances the continued presence of 17-hydroxycorticosteroids in the blood, and 11-oxy-17-ketosteroids in the urine, would denote endogenous cortisol production. The clinical response to withdrawal of maintenance therapy also indicates the patient's capacity to survive without it. Furthermore, during its deprivation, any accessory adrenal tissue will be released from the suppressing action of exogenous cortisone, although the time required for return of adrenal function after long-term steroid therapy is uncertain (Fredell et al. 1955, Geyer 1958, Vermeulen 1958).

TABLE II—TIME THE PATIENTS WERE ABLE TO WITHSTAND DEPRIVATION OF CORTISONE

Case no.	Days off cortisone	
	Remission	Relapse
1	5½	2¾
2	2¾	2¼
3	3¾	3½
4	3½	3
5	..	4½
6	..	4½

The 11-deoxy-17-ketosteroids, which are mainly metabolites of the androgens of adrenal origin, do not reflect secretion of 11-oxygenated steroids, whether endogenous or from maintenance cortisone. In the absence of functioning adrenocorticol tissue they are not present in significant amounts in the urine (Sim et al. 1960). The possibility of an ovarian source of ætiocholanolone (Plantin et al. 1958) does not arise in our patients, because the ovaries were removed at the time of adrenalectomy.

Our observation that adrenalectomised patients can tolerate cortisone lack for variable periods ranging from 2 to 5 days agrees with that of Lipsett et al. (1957), and Birke et al. (1960). Relapse of cancer was not associated with prolongation of the time patients could withstand withdrawal of maintenance therapy.

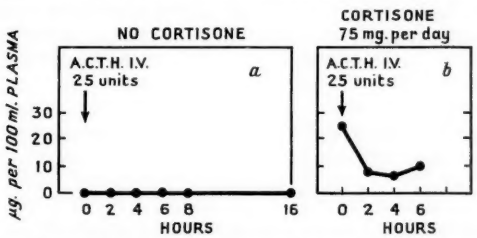

Fig. 4—Effect of corticotrophin on level of 17-hydroxycorticosteroids in peripheral plasma: (*a*) on 3rd day of cortisone-withdrawal, and (*b*) after resumption of cortisone therapy.

The pattern of steroid excretion during the period of cortisone withdrawal was consistent with an absence of functioning adrenocortical tissue. Thus those urinary steroids derived from maintenance cortisone (total 17-ketosteroids and 11-oxygenated fraction) fell to low levels during cortisone deprivation, while 11-deoxy-17-ketosteroids, which are exclusively of endogenous adrenocortical origin, were consistently absent from the urine whether cortisone was taken or not. Furthermore, 17-hydroxycorticosteroids were absent from the peripheral blood on the 3rd day of cortisone withdrawal, and an infusion of corticotrophin did not stimulate their secretion.

These findings, in patients whose cancer had relapsed, were identical with those when the tumour had regressed, and they indicate that relapse of cancer is not associated with the development of functioning adrenocortical tissue.

The small amounts of pregnanediol in the urine of our patients are quantitatively similar to those in the patients studied by Strong et al. (1956), and they are probably of

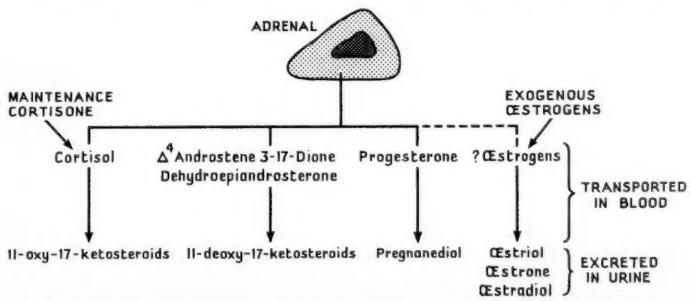

Fig. 5—Steroid hormones and their metabolites of adrenocortical origin.

little significance. They were not affected either by withdrawal of maintenance cortisone or by the clinical state of the cancer.

The detecton of significant amounts of œstriol, œstrone, and œstradiol-17β in the urine of our patients, despite the absence of other evidence of accessory adrenocortical function, confirms our previous findings (Hobkirk et al. 1959), and indicates that the presence of Kober chromogens in the urine of adrenalectomised-plus-oophorectomised patients is not evidence of residual adrenocortical tissue. It is now well established that these chromogens are present in the urine of a proportion of women with breast cancer after adrenalectomy and oophorectomy (Strong et al. 1956, Bulbrook and Greenwood 1957, Bulbrook et al. 1958a and b, McAllister et al. 1960), although their significance and source is still in doubt. In the three patients in whom œstrogen estimations were performed during remission and subsequent relapse of the cancer, no increase was noted during the relapse.

Conclusions

These findings indicate that relapse of mammary cancer after initial response to adrenalectomy and oophorectomy is not due to the development of *functioning* accessory adrenocortical tissue, a conclusion supported by the failure to demonstrate adrenal rests postmortem in the two patients examined. Even if accessory adrenal tissue does develop after surgical removal of the main adrenal glands, the tests described here clearly indicate that its function is suppressed by maintenance cortisone, and that it cannot contribute to the reactivation of tumour growth which inevitably takes place. The failure of pituitary destruction to influence the final relapse in our patients suggests that neither is this due to dependence on a pituitary hormone.

It seems justifiable to assume that the temporary nature of the response to adrenalectomy and oophorectomy results from the ability of the cancer cell to resume active growth in the absence of hormonal factors.

We wish to thank Prof. C. F. W. Illingworth for allowing us to carry out this investigation in his unit. These cortisone-withdrawal studies made extra demands on the resident and nursing staff, and we acknowledge our debt for their assistance. The postmortem examinations were performed by Dr. A. T. Sandison of the University Department of Pathology, Western Infirmary. We also thank Mr. R. A. McAllister, Miss Eleanor Lunney, and Mr. Neal Carlin for technical assistance.

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BEDSORES

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THERE is some evidence that the only pressure sore which is potentially or actually lethal is the one which causes necrosis of muscle and/or subcutaneous tissue. Once such a sore has developed it is extremely refractory to treatment and even to major surgery. We have therefore concentrated our attention upon the prophylaxis of bedsores. In the unconscious patient especially, this is a major medical and nursing problem.

Within limits, the more often patients have their position changed the less likely are pressure sores to develop; so certain special units have adopted routines of 2-hourly or hourly turning of patients, with particular attention to their backs and other pressure points. The difficulty of maintaining such schedules in general and geriatric hospitals, and the near-impossibility of achieving them for patients nursed at home, has led to a search for a method which would automatically reproduce the beneficial effects of turning the patient.

Several "alternating pressure" mattresses are produced commercially in various Western countries. The first was made in the United States as an apparatus for mechanically redistributing the weight of the patient over

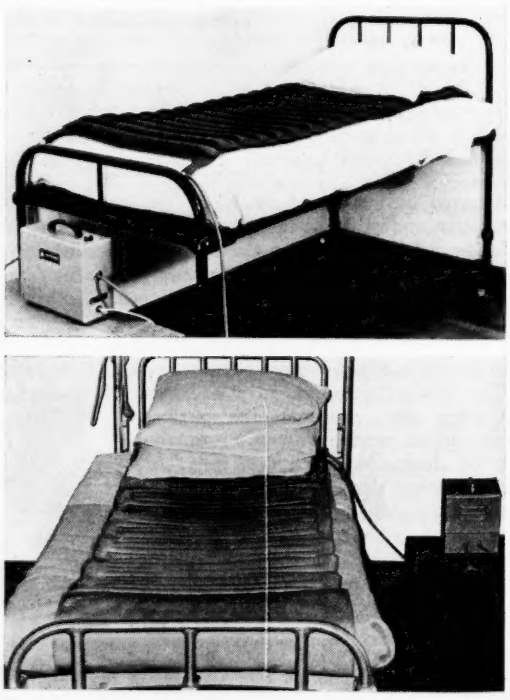

Fig. 1—Two types of alternating-pressure mattress on sale in this country.

a wider area than the normal pressure points. The different mattresses vary slightly in construction and in the materials used. But they all consist essentially of a sectional mattress of impervious material inflated by an air pump, which automatically controls adjacent " air cells " in alternating cycles of 2–5 minutes. None that we have used so far has proved entirely reliable or satisfactory in use over a long time, despite the manufacturers' claims to the contrary.

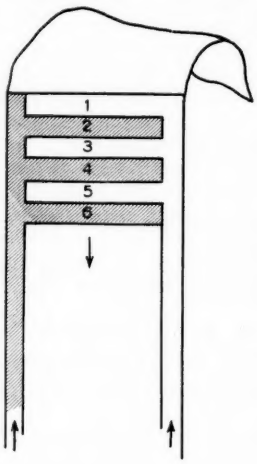

Fig. 2—Schematic representation of one form of alternating-pressure mattress.

Alternating-pressure mattresses (fig. 1) are made of stout polyvinyl-chloride sheet, or of rubber-impregnated fabric, and all are slightly narrower than the standard hospital mattress upon which they are placed. They are held in position by flaps at both ends which tuck under the standard mattress at the head and foot of the bed. The air cells run either longitudinally or transversely. In the type we used for our experimental work the sections, $1^1/_4$ in. (3·125 cm.) in diameter, run transversely across the width of the mattress. They are interconnected to form two parallel systems which open alternately into two common ducts, each of which runs longitudinally along one edge of the mattress. These ducts are connected by pressure tubing to a pump driven by an electric motor. The two systems are inflated and deflated alternately in a cycle of 4 minutes so that the patient's body is supported in turn by odd and even numbered sections (fig. 2). There are forty-two sections, and, as shown in fig. 3, the weight of the patient is supported at all times by one or other system because the cycles are timed to overlap so as to obviate any period of low pressure in both systems.

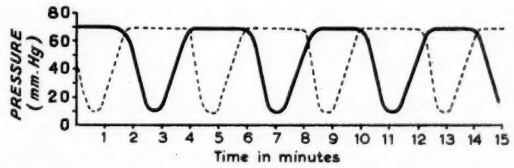

Fig. 3—Pressure cycle in air cells of an alternating-pressure mattress.

We have carried out a series of experiments over the last few years at the geriatric unit of the Cowley Road Hospital, Oxford, in an effort to establish some of the practical requirements for an alternating-pressure mattress. The work is continuing, and this is an interim report. A number of modifications to all the available pieces of apparatus are still necessary.

An experimental mattress was constructed which recorded the pressure at the point when the patient ceased to be supported on a cushion of air, and with it the pressure was measured with various somato-types of patients in different positions. Strips of copper were incorporated into the opposing surfaces of every section of an alternating-pressure mattress, and into two electric circuits, so that on contact a numbered bulb on a control panel was lit, indicating the air cell in which the contact was made. By means of two mercury manometers mounted on the panel the air pressures in both pneumatic systems could be read at any time in the cycle (fig. 4).

Thus the part of the body under which the contact occurred could be identified, and the pressure at this time could be read directly. This pressure was defined as the " bottoming " pressure. Fig. 5 shows the relation

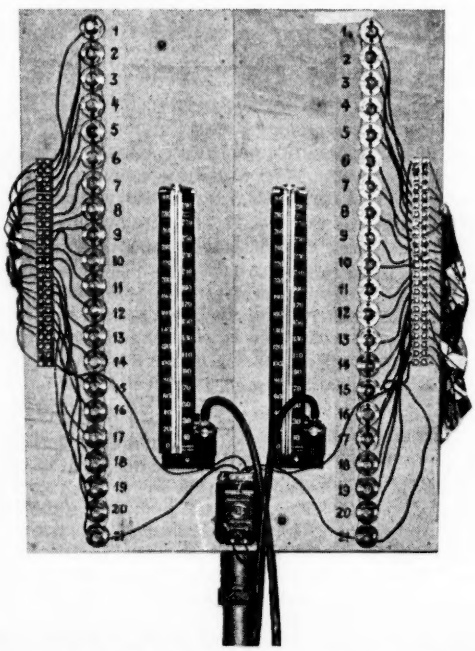

Fig. 4—Control panel of apparatus connected to experimental mattress.

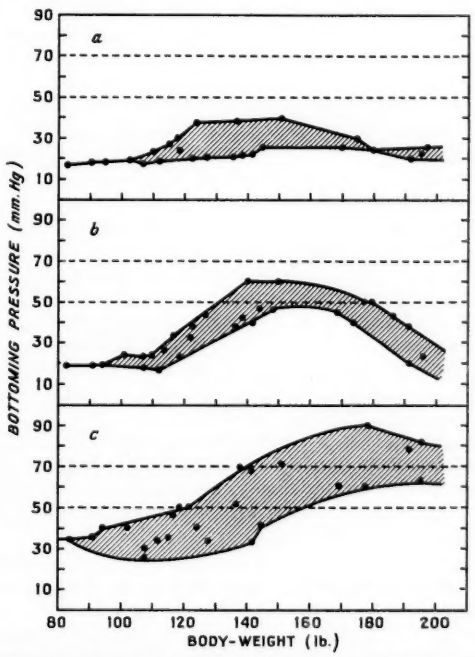

Fig 5—Relation between bottoming pressure and weight of patients (*a*) With light patients (83–119 lb., or 37·7–54 kg.), (*b*) with patients of medium weight (122–145 lb., or 55·3–65·8 kg.), and (*c*) with heavy patients (151–311 lb., or 68·5–141 kg.).

between the bottoming pressure and the weight of the patient. The readings were taken with the patient supine, and in almost all cases bottoming occurred over the sacral area.

If all, or a large part, of the weight of the body is supported upon such a prominent point as the elbow or heel, very high pressures are recorded; and this, coupled with the fact that movement of the limbs may produce shearing strains, accounts for pressure sores being common in these areas. If care is taken to ensure that the patient's position does not produce these high pressures, and rubbing movements of the pressure points over the bedclothes are avoided, a pressure of 40 mm. Hg is sufficient for any patient in the prone or supine position. In the lateral or sitting position, however, a pressure of 50 mm. Hg is required for light patients, 70 mm. Hg for medium patients, and up to 90 mm. Hg for heavy patients. The tendency for patients nursed in the prone position to support the weight on an arm or knee must be especially remembered, because this often causes very high pressure in these areas.

In the supine or lateral position the bottoming pressure tends to increase in patients of light or medium weight, but in heavy patients the bottoming pressure tends to decrease. This is probably because in heavier patients the bony points are less prominent, because of greater muscular development or increase in the layer of subcutaneous fat. When sitting the increase in bottoming pressure tends to run parallel with increase in the patient's weight.

Correlation between body types and bottoming pressures is not very close, but in thin patients with prominent bony points the pressures tended to be higher than in muscular or well-covered patients in the same weight range. The three heaviest patients in our series showed bottoming pressures well below the mean level, but they were all obese small-boned females. This is not surprising because the pressure imposed by a weight on any surface is inversely proportional to the area of contact. Thus, since it increases the patient's comfort, it is advisable to use the alternating-pressure mattress at no more than the pressure which avoids bottoming, but care must be taken to ensure that the pressure used is high enough for the thin angular type of person.

When the sitting patient assumes a more upright position the bottoming pressure increases very much under the ischial tuberosities, until in the upright (90°) position the pressures are very high indeed. Up to an angle of inclination of 60° from the horizontal, however, the pressures do not rise above 90 mm. Hg, and they are usually much less. Whenever patients who cannot move freely are propped up in bed, this rise in pressure under the ischial tuberosities should be remembered; and these cases should not be nursed at an angle of inclination greater than 60° from the horizontal if this can be avoided. The danger of producing pressure sores in elderly immobile patients, even when they are sitting out of bed, should also be realised.

Our apparatus was not accurate enough to compare the results using various types of base mattress. Nevertheless the differences between a good-quality base mattress compared with a hard wooden base suggest that, within limits, the more resilient the base upon which the alternating pressure mattress is placed the more effective it will be. This should be borne in mind if it is thought advisable, during the day, to seat the patient on an alternating-pressure mattress placed on a chair, when it seems very unwise to use an unyielding base, such as a wooden chair, rather than a soft upholstered one.

Conclusion

Our experience with an alternating-pressure mattress in practice suggests that it will ultimately be valuable in the prevention, and possibly also in the treatment, of pressure sores. It certainly saves a lot of nursing time; but much remains to be done before an entirely satisfactory apparatus can be produced for a controlled clinical trial. Current work is being directed towards correcting the deficiencies shown in all the pumps and motors of the alternating-pressure mattresses we have tested, but we are satisfied that the principle is sound.

Our work is to be published in detail elsewhere; but we feel that this abbreviated account may be helpful to other workers, and may prevent the misuse of the alternating-pressure mattresses at present on the market.

A FAMILY WITH AN XXXXY MALE, A LEUKÆMIC MALE, AND TWO 21-TRISOMIC MONGOLOID FEMALES

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WE have found, in one family, an XXXXY male, two 21-trisomic females with mongolism, and a leukæmic male. The propositus was the XXXXY male, who was discovered by routine sex-chromatin testing of the population of a mental-deficiency institution. Three sex-chromatin masses were present in about 14% of the cells of several buccal mucosal smears, which were stained by the Feulgen reaction (fig. 1). Chromosome studies were made on repeated blood-cell cultures. Karyotype analysis is compatible with an XXXXY sex-chromosome complement and a somatic chromosome number of 49 (fig. 2).

The 21-year-old propositus has severe mental retardation, with an intelligence quotient of 21. He has a cleft palate, strabismus, multiple abnormalities of the skeletal system, and eunuchoidism. He is 5 ft. $4^1/_2$ in. (164 cm.) tall, with a floor-to-pubis measurement of 3 ft. $1^1/_2$ in. (95 cm.). His voice is unbroken. He has no facial or axillary hair, and very scanty pubic hair. The penis is small, about 3 cm. in length, but otherwise normal. The small scrotum contains a mass about 1 cm. in diameter on the left, but only cord-like structures are palpable on the right. Urinary 17-ketosteroid excretion is low (2·8 mg. per day), and urinary follicle-stimulating hormone excretion is normal (positive at 13 and negative at 52 units per day).

Fig. 1—A chromatin-three-positive nucleus of a cell from the buccal mucosa of an XXXXY male. (Feulgen stain. ×1500.)

The father of the propositus died of chronic lymphatic leukæmia at 45. He was chromatin-negative by the blood-

Fig. 2—An XXXXY male. A metaphase plate from a blood-cell culture is shown on the right. The karyotype prepared from this plate is on the left. (Acetic orcein stain. ×1000.)

smear technique, but this was based on examination of only 300 cells, and the presence of a shift to the left, with a Cook-Arneth index of 2·10, almost negates the significance of this finding.

Chromosome studies have been made on blood-cell cultures obtained from several relatives. The patient's mother has a normal female karyotype, with a somatic chromosome number of 46 and two X chromosomes. She is chromatin-positive. The brother of the propositus is chromatin-negative and has a somatic chromosome number of 46 with an XY sex-chromosome complement. The sister of the propositus is chromatin-positive; her chromosome studies have not been completed.

The propositus had three paternal aunts. One of these three sisters has mongolism. Another sister has three daughters of whom the youngest has mongolism. Both mongols have classic facies, short stature, scoliosis and lordosis, short forearms, short broad hands with large *atd* angles (73°, 74°, 86°, and 88°), and intelligence quotients in the imbecile range (30 and 41). Each has other features which help to make the diagnosis of mongolism certain.

Chromosome studies have been made on both mongols, and on the normal aunt of the propositus who is the mother of one of the mongols. The normal aunt has a normal female karyotype. Both mongols have a somatic chromosome number of 47, with the extra chromosome in groups 21–22 which probably represents 21-trisomy. These females are all chromatin-positive and have 14 chromosomes in groups 6-12+X—i.e., they have two X chromosomes.

The concentration of abnormal karyotypes in this family is worthy of note. So is the presence of chronic lymphatic leukæmia in one member whose karyotype could not be determined. But, since he had two normal children (one male and one female) as well as an XXXXY son, he probably had a normal male karyotype.

The production of an XXXXY child by parents with normal karyotypes could be explained by either meiotic or mitotic nondisjunction. In the absence of evidence of chromosomal mosaicism, meiotic nondisjunction seems more likely. Three events are required: either a single nondisjunctional event in the mother and two successive nondisjunctional events in the father, or two in the mother and one in the father. There are two reasons for suspecting that the repeated nondisjunctions were in the father. First, he was 32 when his XXXXY son was born, whereas the mother was only 23, and meiotic nondisjunction seems to be more frequent with advancing age. Second, two paternal relatives seem to have had meiotic nondisjunctions, leading to the two cases of 21-trisomy. A predisposition to nondisjunction in three of the members of this family would thus account for all the cases of trisomy or polysomy. The effect of advancing age is also apparent: the mongols were born when their mothers were 34 and 36 years old.

A fuller report of this family is being prepared. It will include more clinical data, pictures of the affected individuals and their karyotypes, and the quantitative data supporting our contention that chromosomal mosaicism is not present in the affected members of the family.

There was no evidence of chromosomal mosaicism in the probable XXXXY male reported by Fraccaro and Lindsten (1960).

This work has been supported by grants from the U.S. Public Health Service (RG-7608 and M-4386[A]), the Josiah Macy, Jr., Foundation, and the National Association for Retarded Children.

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Preliminary Communications

CAROTID ARTERIES, BLOOD-PRESSURE, AND STROKES

Dickinson and Thomson [1–3] have perfused internal-carotid and vertebral arteries in cadavers, and have reported a strong negative correlation between antemortem blood-pressure and rate of flow of perfusion fluid. Subjects with malignant hypertension or renal hypertension differed significantly from those with essential hypertension, and subjects with strokes all had low flow-rates in the carotids and vertebrals. These workers suggested that essential hypertension and strokes are manifestations of the same underlying disturbance—namely, a reduced "fluid carrying capacity" of the main vessels supplying the brain.

Their technique of perfusion has been criticised elsewhere.[4 5] When allowance has been made for variations in the sizes of cannulæ used, the data do not demonstrate any difference between renal and essential hypertension, but the differences between subjects with strokes, with malignant hypertension, and with essential hypertension remain even after correction for sizes of cannulæ. The measurements were made under experimental conditions very different from those obtaining in vivo—i.e., rate of flow and pressure gradient were much higher, and the mean pressure in the arteries was much lower, than in life—and some supporting evidence is required before the findings can be accepted as having physiological significance.

1. Dickinson, C. J., Thomson, A. D. *Lancet*, 1959, ii, 46.
2. Dickinson, C. J., Thomson, A. D. *Clin. Sci.* 1960, **19**, 513.
3. Dickinson, C. J., Thomson, A. D. *ibid.* 1961, **20**, 131.
4. Lowe, R. D. *Lancet*, 1961, i, 825.
5. Lowe, R. D. *Brit. med. J.* 1961, i, 1109.

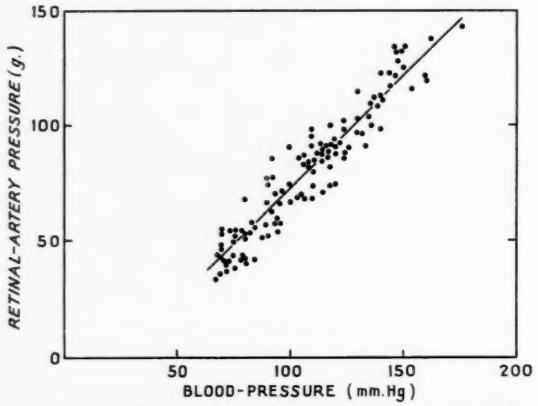

Fig. 1—Relation between diastolic ophthalmodynamometer reading, in grammes, and diastolic brachial-artery pressure in 118 patients.

Such evidence would be provided by comparing pressure measurements in the aorta and in the circle of Willis in living subjects. It is not feasible to measure directly the pressure in the circle of Willis, but a comparison of retinal-artery pressure and brachial-artery pressure should

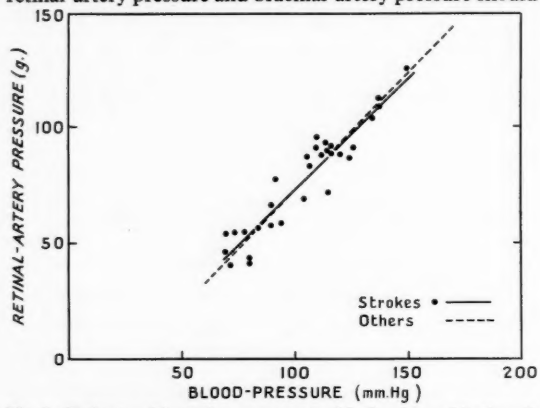

Fig. 3—Patients with strokes compared with the slope of "others".

be a reasonable substitute, because the retinal artery arises from the ophthalmic branch of the internal-carotid artery. If Dickinson and Thomson's findings are physiologically significant, the ratio of retinal-artery pressure to brachial-artery pressure should be highest in normal subjects and in those with malignant hypertension, intermediate in

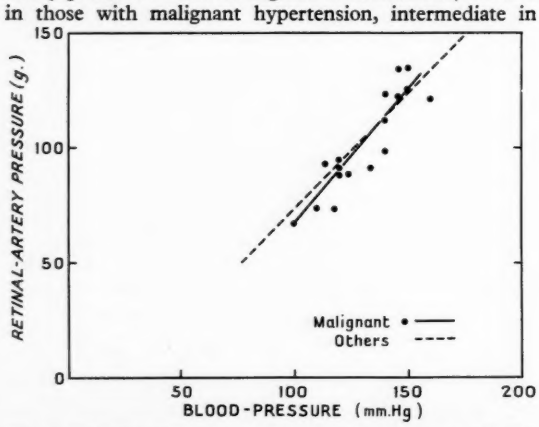

Fig. 4.—Patients with malignant hypertension compared with the slope of "others".

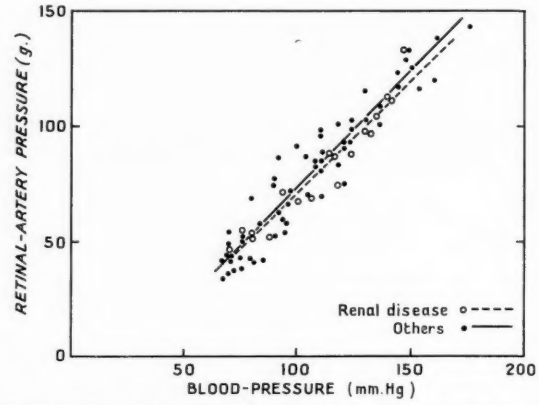

Fig. 2—Patients with renal disease compared with "others" (i.e., those with essential hypertension and normals).

those with renal hypertension, and lowest in subjects with essential hypertension or strokes.

I have measured brachial-artery pressure and retinal-artery pressure in 118 patients as part of an investigation of carotid occlusion.[6] The diastolic pressure of the retinal artery was measured by Bailliart's ophthalmodynamometer, and the blood-pressure by sphygmomanometer. Severe renal disease was present in 18 patients (polycystic kidney 5, chronic nephritis 6, chronic pyelonephritis 5, and renal-artery stenosis 2); 13 of these were hypertensive, and the renal disease was thought to be the cause of the hypertension. 17 patients had malignant hypertension with papillœdema, hæmorrhages, and exudates in the optic fundi, recorded in each case by an independent observer. 31 patients had had a stroke but were considered not to have carotid stenosis.

RESULTS

Fig. 1 shows the results from all 118 patients. In figs. 2, 3, and 4 renal disease, strokes, and malignant hypertension are compared with "others", comprising normals and cases of essential hypertension. No significant difference is found in the slopes, or in the position of the slopes in all four groups of patients.

These findings become more significant after calibration of the ophthalmodynamometer readings to give true retinal-artery pressure in millimetres of mercury. This has been done from calibration curves obtained from five cadavers. Their validity has been tested by comparing

6. Lowe, R. D., Stephens, N. L. *Lancet*, 1961, i, 1241

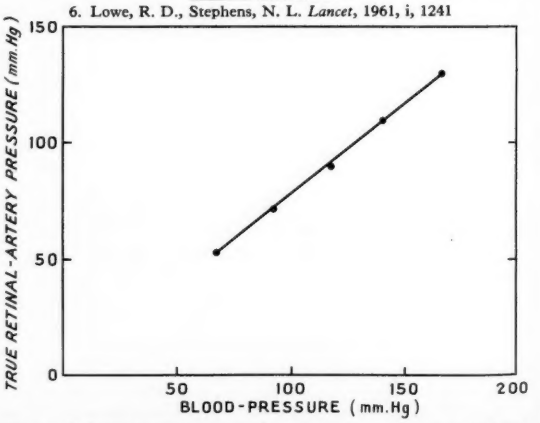

Fig. 5.—Relation between true retinal-artery pressure (mm. Hg) and brachial-artery pressure, using the fitted straight line from fig. 1.

curves on rabbits before and after death, and no significant difference was found between the two. Fig. 5 shows the result of replotting the straight line from fig. 1, assuming an average resting intraocular pressure of 17 mm. Hg. The retinal-artery pressure remains at about three-quarters of the brachial-artery pressure throughout the range of patients.

CONCLUSIONS

These results conflict with those of Dickinson and Thomson. They provide no evidence that increased resistance in the carotid vessels is commonly the cause of strokes or essential hypertenson. There is some increase in resistance between the aorta and the retinal artery as the result of hypertension, and some of this increase may be in the carotid vessels, but it is clearly an unimportant factor in regulating blood-flow to the brain.

It seems likely that Dickinson and Thomson's results on carotid arteries in cadavers were an artefact of the method of investigation used, and that they do not represent changes of physiological significance in vivo. Although I have not been able to test their conclusions for the vertebral arteries, the same criticism probably applies to these.

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A NEW DIAGNOSTIC APPROACH TO MUCOSAL INFLAMMATION IN PROCTOCOLITIS

IN the diagnosis of inflammatory disorders of the rectosigmoid, mucosal-biopsy techniques hitherto employed [1 2] seem inconvenient for routine use. Moreover, by analogy with cutaneous inflammatory processes [3 4] evaluation of inflammatory states in this region according to the cytology of mucosal secretions seems likely to prove more informative. A swab technique has been attempted, but has not yielded satisfactory preparations in our hands.

We have developed a method for qualitative and semi-quantitative cytological examination of the mucosal secretions from the rectum and the distal part of the colon within reach of a sigmoidoscope. The principle of the method is that an imprint is procured from a circumscribed area of the mucosa.

TECHNIQUE

Circular glass discs, 14 mm. in diameter and 0·8 mm. thick, are mounted on ordinary corks of corresponding size with polystyrol cement (fig. 1A). To obtain sufficient adhesion during the brief contact with the mucosa, the discs are coated with a weak protein solution (human serum or egg albumin). A sampling unit, consisting of a cork with mounted glass disc, is fastened in the grip of a tampon holder corresponding to the sigmoidoscope employed. With the sigmoidoscope used by us, the dimensions given above allow the passage of the greatest possible disc area.

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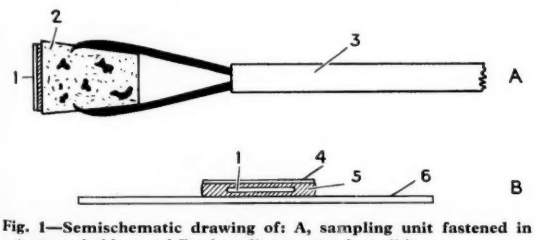

Fig. 1—Semischematic drawing of: A, sampling unit fastened in tampon holder; and B, glass disc mounted on slide.

1, Glass disc; 2, cork; 3, tampon holder; 4, cover-slip; 5, mounting medium; 6, slide.

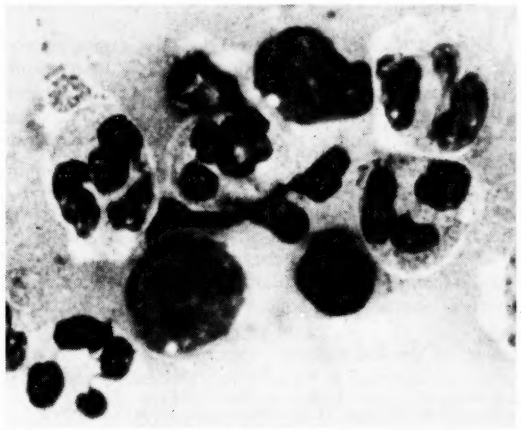

Fig. 2—Sample from patient with moderate proctocolitis, showing mostly neutrophil granulocytes, but also a few lymphocytes and macrophages.

Patients are given no enemas or laxatives in the few days before sigmoidoscopy. The sigmoidoscope is inserted until the mucosal area concerned is seen more or less parallel to the opening of the instrument. After removal of the light source, a sampling unit is introduced through the tube with the aid of the tampon holder until the glass disc rests lightly against the mucosa. The unit is held in this position for five seconds and then withdrawn. It is important that any movement of the glass disc against the mucosal surface is avoided during the procedure.

The sample is allowed to air-dry and is stained with May-Grünwald-Giemsa stain. The disc is finally mounted on a slide, sample side upwards, and the disc covered by a cover slip (fig. 1B).

RESULTS

By this method we have examined 42 subjects without symptoms or signs of proctosigmoidal disease. In all the preparations from healthy subjects the picture was characterised by mucus strands, bacteria, and scattered, desquamated, partly autolysed epithelial cells.

In a few cases inflammatory cells were found singly or in isolated, small clusters.

Fig. 2 shows a specimen from a patient with moderate proctocolitis. Here there were large numbers of inflammatory leucocytes — mostly neutrophil granulocytes, but also a few lymphocytes and macrophages. In this case no mucosal changes were seen through the sigmoidoscope.

So far 15 patients with proctocolitis have been examined. In all cases, including those in which no mucosal changes were visible macroscopically, inflammation was evident in the microscopic picture of the mucosal secretions. Thus no difficulties have been encountered in distinguishing normal from pathological specimens.

In most of the patients with proctocolitis who have been examined, the cytological picture has been characterised by large numbers of eosinophilic granulocytes. In these cases a specific cause of the mucosal inflammation seems possible, but the number of patients examined is still too small for any conclusions to be drawn.

DISCUSSION

Compared with this cytological method, direct macroscopic evaluation of the rectosigmoidal mucosa through the sigmoidoscope seems coarse. The discrepancy between the sigmoidoscopic finding and the cytological picture (fig. 2) supports this assertion. In cases of proctocolitis the cytological method has been found to reveal distinct inflammatory changes in the mucosal secretions from patients with proctocolitis of so slight a degree that no abnormality is detectable by sigmoidoscopy.

The ability of the present method to disclose even slight inflammatory conditions makes it suitable for follow-up studies of patients with different types of proctocolitis. Furthermore, this method may enable the ætiology of the inflammatory processes to be elucidated.

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THE HELIUM-OXYGEN TEST

A New Technique for Identifying Small Left-to-right Shunts

LEFT-TO-RIGHT shunts constitute the majority of surgically correctable congenital cardiac defects. Blood-oxygen determination during " right " heart catheterisation is the technique most widely used to localise and quantitate left-to-right shunts. Using this technique accurately, with careful sampling [1] and the best equipment, shunts as small as 15% can be detected in cooperative patients. But in children the oxygen content may vary rather widely during catheterisation, making the certain detection of small left-to-right shunts extremely difficult.

More sensitive tests have been developed using two different principles:

The first is the arteriovenous difference of an inhaled inert gas, such as nitrous oxide [2 3] or radioactive krypton. The gas contents of simultaneous blood samples drawn from various sites in the right heart are compared with those of peripheral arterial samples.

The second is the lung to right-heart circulation-time. The indicator is introduced into the left side of the heart via a catheter [4] or by inhalation. Blood samples are taken from the right heart, giving a time-concentration curve of the indicator. Peripheral arterial samples are not necessary. Cardiogreen and radioactive gas [5–8] have been used as indicator substances. If a radioactive gas is used, complex equipment is usually necessary, and precautions have to be taken to prevent contamination of the room. The use of hydrogen [9] allows intracardiac recording of hydrogen-ion concentration by an electrode catheter without the necessity of blood sampling, but special equipment is necessary, and precautions have to be taken to prevent explosions. The use of a readily available indicator gas—stable oxygen—is safe and does not require special equipment if the laboratory is equipped for oximetry.

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PRINCIPLE

The blood-oxygen saturation in the " left " heart is temporarily depressed by inhalation of an inert gas. We use 100% helium because it is inexpensive, readily available, and highly diffusible. From a selected site in the right heart blood is drawn via a catheter at constant speed through an oximeter. Changes in blood-oxygen saturation are thus recorded continuously. After the patient has inhaled 100% helium four to eight times, 100% oxygen is given. The time for oxygen to appear in the right heart, as shown by a rapid rise in blood-oxygen saturation, is distinctly shorter when sampling downstream from a left-to-right shunt. The test can be repeated almost immediately at different sites in the right heart to localise the shunt.

The presence of a left-to-right shunt, as shown by this technique, was confirmed by methyl-iodide inhalation studies [6] or by right-heart sampling after injection of cardiogreen dye into the pulmonary artery.[4]

METHODS

Helium is given to the patient by way of a Rubens valve. The patient breathes through a mouthpiece, and the nasal air passages are closed with a nose clamp. The patient can be switched from 100% helium to 100% oxygen by means of a two-way valve and " Y " connector incorporated in the system. The blood is drawn through an oximeter at a fixed rate by a constant-speed withdrawal pump, as commonly used for recording dye-dilution curves.

RECORDING EQUIPMENT

Throughout the procedure whole blood is sampled continuously from the intracardiac catheter, using a constant-

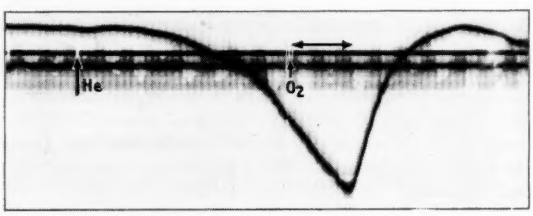

Fig. 1—Oxygen-concentration curve from femoral artery.
Administration of helium and oxygen is indicated by arrows. Note sharp fall and rise.

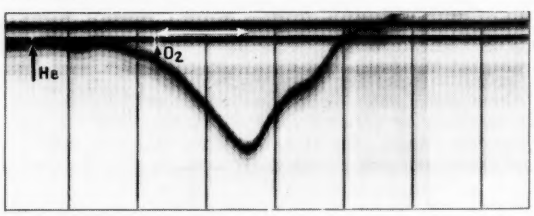

Fig. 2—Oxygen-concentration curve from right heart in patient with large left-to-right shunt.
The curve is similar to the femoral artery curve.

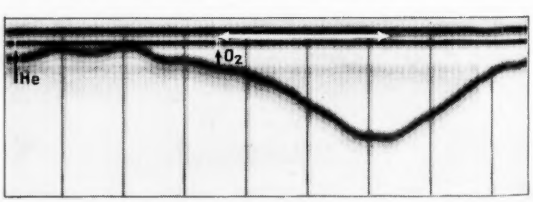

Fig. 3—Flat curve from right heart, with late appearance of oxygen, in patient without left-to-right shunt. (Normal " venous return " of oxygen.)

withdrawal pump,* at a rate of 7·64 ml. per minute. The blood is drawn through a cuvette oximeter,† and the deflections are recorded photographically by a galvanometer-recording system.‡ Single-scale oximetry is used throughout. The baseline is set with constantly flowing blood from the right-heart chamber or vessel in which the catheter tip is placed, and the decreasing oxygen saturation is recorded as a downward deflection. A marking device § records the exact time of stopping and starting administration of helium, and of giving 100% oxygen. The recording speed is set at 5 mm. per second. Helium is not given until the initial baseline, set with blood flowing constantly through the cuvette oximeter, is steady. At the end of the study the saturation either returns to or slightly exceeds the original saturation. An instant self-developing photokymograph ‖ allows inspection of the curves immediately after the procedure.

INTERPRETATION OF CURVES

In several patients oxygen-saturation curves were obtained from the femoral artery. After a few breaths of helium the oxygen saturation falls rather quickly, after oxygen a sharp rise is noted (fig. 1). After longer administration of helium a desaturation plateau is reached. Repeat studies on the same

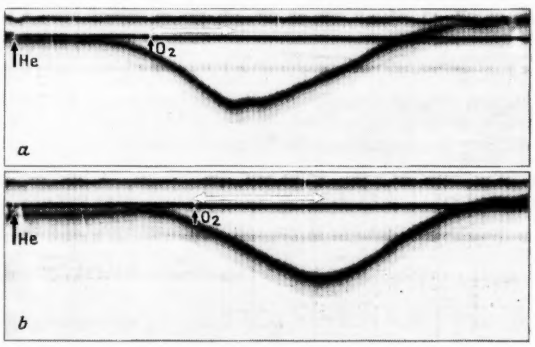

Fig. 4—(*a*) Curve from right ventricle in patient with small left-to-right shunt, not detected by conventional oximetry. (Note short appearance time of oxygen.) (*b*) Normal venous return from right atrium in the same patient.

patient have shown that the appearance-time of oxygen is constant if the rate of sampling remains unchanged.

In the presence of a left-to-right shunt the oxygen-saturation curve from the right heart is similar (fig. 2). Repeat studies on the same patient have shown that the decrease in oxygen saturation depends somewhat upon the respiratory rate and the duration of helium inhalation; but the appearance-time of oxygen, which is foreshortened by the shunt, remains constant.

In the absence of a left-to-right shunt a " venous return " curve is obtained (fig. 3). The " build-up slope " and " disappearance slope " of this curve is considerably flatter than that of the left-to-right shunt curve. The oxygen appearance-time is distinctly longer, and the sharp peak of the left-to-right shunt curve is missing.

Thirteen patients have been examined by this technique. A left-to-right shunt was twice established by this method despite inconclusive oxygen values from serial sampling in the right heart. The right-heart catheterisation data of one of these patients is as follows:

	O_2 *saturation* (%)
Superior vena cava	78
Inferior vena cava	85
Mid right ventricle	82
Main pulmonary artery	79
Mid right ventricle	80
High right ventricle	81
Brachial artery	96

*Infusion-withdrawal pump, model 600–900, manufactured by Harvard Apparatus Company, Inc., Dover, Mass.
†Simultaneous single and double scale oximeter XC-50B, manufactured by the Waters Corporation, Rochester, Minn.
‡Single scale galvanometer XG-70B, and control assembly XP-70A, from the Waters Corporation.
§Marking device RMD-1, manufactured by the Waters Corporation.
‖Manufactured by the Waters Corporation.

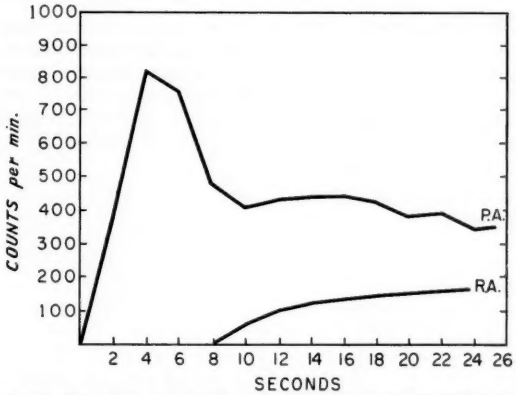

Fig. 5—Same patient as in fig. 4. Radioactive-methyl-iodide inhalation confirms the presence of a left-to-right shunt (immediate appearance of radioactivity at pulmonary-artery level, with normal venous return in right atrium).

Fig. 4 shows oxygen-concentration curves at the site of the shunt and proximal to the shunt after helium inhalation. The distinct difference in oxygen appearance-time in the right atrium and right ventricle establishes the presence of a left-to-right shunt. In both cases this finding was confirmed by inhalation of radioactive methyl iodide (fig. 5).

DISCUSSION

Most specialised tests for the detection of small left-to-right shunts require complex equipment, knowledge of radioisotopes, and special precautions to protect patient and operators. This is not necessary when a stable gas, such as oxygen, is used. By inhalation of 100% helium, transient hypoxia is produced. Since the patient is breathing carbon dioxide in and out normally, he does not experience the urge to breathe faster and is unaware of the lack of oxygen. The period of hypoxia is so short that none of the patients examined has had cerebral symptoms. The oxygen content in the femoral artery was once depressed to a plateau which caused slight " light headedness ". During the test the electrocardiogram may show some tachycardia, but no other changes have been observed.

This test is most useful in detecting small left-to-right shunts, and complications would not be expected in these relatively healthy patients.

After an oxygen-saturation curve has been recorded from one cardiac chamber, the catheter can be withdrawn and repeated studies can be made at different sites almost immediately. The well-known " background " problem of dye and radioactive indicators does not arise. The diagnosis can be established by means of a single catheter in the right heart, without arterial samples. At present quantitative assessment is not feasible. However, since this test can detect small left-to-right shunts which are not conclusively demonstrable by changes in blood-oxygen saturation alone, it is presumably capable of detecting small shunts of less than 15–20%.

SUMMARY AND CONCLUSION

A simple test can detect small left-to-right shunts during cardiac catheterisation.

Oxygen is used as an indicator gas to determine the lung to right-heart circulation-time. It is given after the blood-oxygen concentration in the left heart has been depressed by inhalation of 100% helium. Early appearance of oxygen in the right heart indicates a left-to-right shunt.

The test is considered safe for acyanotic patients, and it can be performed in any cardiac catheterisation laboratory equipped for cuvette oximetry. No additional instrumentation or safety precautions are necessary.

Left-to-right shunts were twice detected which were not demonstrable by the usual serial blood-oxygen saturation determinations.

This work was supported by a grant from the Minnesota Heart Association.

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Reviews of Books

The Transplantation of Tissues and Organs

MICHAEL F. A. WOODRUFF, M.D., M.S., F.R.C.S., F.R.C.S.E., F.R.A.C.S., professor of surgical science in the University of Edinburgh. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961. Pp. 777. 204*s*.

IF the nature of the homograft rejection phenomenon can be elucidated and a harmless method of avoiding it discovered, a new era of reconstructive surgery will begin. But possible clinical gain is only one of the reasons why more and more research-workers all over the world are turning to tissue transplantation. There are many fundamental questions to be answered: problems of regeneration and growth, problems for the geneticist and immunologist, and problems in other branches of biology in which transplantation is proving a useful tool. In anticipation of the final break-through, some workers are studying methods of storage and preservation of tissue, while others are devising techniques for transplanting organs such as the heart, the liver, and even the whole head. The literature is vast and many important discoveries have already been made. Professor Woodruff has tried to cover exhaustively all aspects of this rapidly expanding subject, and, apart from a chapter on corneal grafting (by Prof. George Scott) and a section in the chapter on bone-grafting (by Mr. Norman Nisbet), this book is entirely his own—a tour de force.

The first third is a detailed consideration of the basic principles underlying auto, homo, and hetero transplantation and is particularly well done. For the first time the world literature has been collected, sifted, arranged in logical order, and presented as a readable narrative. But Professor Woodruff does more than collate; in addition to a critical appraisal of past work, he indicates possible lines of future research. This part alone makes it an essential work of reference for anyone interested in tissue transplantation. The remainder of the book contains sections on every tissue or organ which has ever been used as a transplant, and the author goes into the territory of plastic, orthopædic, cardiovascular, genito-urinary, and gastro-intestinal surgery. At first sight operations such as orchidopexy and gastrojejunosomy seem out of place, but they *are* examples of transplantation and illustrate how thoroughly Professor Woodruff, once committed, has explored the subject.

The references alone occupy 110 double-columned pages of small type. It is obviously impossible to produce virtually single-handed a book of this kind and keep it up to date at the time of publication, so comparatively few references are after 1957. But, up to 1957, the work is encyclopædic and will save research-workers many weary hours. The illustrations are few, and some (for example, those dealing with plastic operations) are ill-chosen. But it would be very wrong to emphasise minor faults in a book that deserves the highest commendation.

Pain

F. J. J. BUYTENDIJK, professor of psychology, University of Utrecht. Translated by EDA O'SHIEL. London: Hutchinson. 1961. Pp. 180. 25*s*.

ALL animals suffer injury at some time, but whether they feel pain, its intensity, the response to it, and its aftermath depend on the development of the central nervous system. Where memory is lacking there can be no pain, but only a reflex response to injury. Pain is still undefinable and its significance a problem; thus any book on the subject is likely to stimulate thought. This book is no exception, though many readers may disagree with some of its statements, several of which seem unclear, too emphatic, or contradictory. Professor Buytendijk apparently disagrees with the suggestion that pain is useful in preventing self-injury and seems to hold that pain is disagreeable because it indicates a dissolution of part of the self. But it is ordinary experience that pain is a warning that an act is harmful, and those who are insensitive to pain can be fully aware through other channels that the self is injured, yet they do not suffer from that knowledge. Again, rather than state that "pain breaks a man in body and soul", it would be more accurate to say that total absence of sensation does just this. Yet it is not clear what the author means by soul, since a few paragraphs later he states that pain does not incapacitate a man's life as a person.

There is some confusion between the physical sensations which give rise to pain and mental states which are called painful. Both physical pain and mental distress have profound effects on the autonomic nervous system, yet the subject has no difficulty in recognising the difference between the two kinds of pain. In fact, the use of the word pain with reference to mental states seems to depend to some extent on the similarity of the visceral responses, and on the complete absence of an exact definition of pain. The author's description of what is painful must be founded on his own experience and is not of general application. To many, a coarse blue dress or a wrong note on a violin mean nothing at all, whereas to others the loud pealing of church bells is anything but qualitatively pleasant, and gives rise to all the emotional reactions associated with pain. Tears can be formed copiously in response to some kinds of not very severe pain—for example, that from a dental drill—at a time when there is little emotional response and certainly nothing which could be described as a surrender; in other words, tears can flow because of a simple anatomical link between a sensory path and the secretomotor paths. On p. 157 the author suggests that we seek pain in order to participate personally in objective events, and mentions that in moments of tension a man may press his fingernails into his palm and bite his lips. But how many people do this to the point of pain? Such movements, and also curling up the toes or holding the breath, are no more than a release of tension, and the tension would have to be almost unendurable before self-inflicted pain was used as a distraction. The author's final conclusion is that pain is intimately connected with the reality of human nature.

The translation from the Dutch is fluent and grammatical, but the proper word has not always been chosen: it is unclear whether marrow in relation to nerves means axoplasm or myelin sheath; the word constrict is used on various occasions and sometimes seems to mean inhibit; and it has not been realised that only some animals, and certainly not bees, have paws.

Anyone interested in the problem of pain should read this book and discover for himself where he agrees or disagrees with the author.

Essentials of Neurology

JOHN N. WALTON, M.D., M.R.C.P., neurologist, Newcastle General Hospital and Newcastle Regional Hospital Board. London: Pitman Medical Publishing Co. 1961. Pp. 422. 30*s*.

THIS compendium of clinical neurology is probably aimed primarily at the final-year student, and it should be very useful to him. Comprehensiveness and brevity, however, are often incompatible, and some sections of the book seem too brief (the neurological complications of endocrine disease, for

example, are covered in one-and-a-half pages; and to deal in similar space with the management of the incurable case hardly allows room for more than a few general remarks). The inclusion of a section on treatment, apart from the mention of therapy in individual disease, is welcome since it may help to dispel the illusion that neurology is entirely diagnostic; but 40 pages, including surgical treatment and mental disorder, again proves too short to avoid at times misleading brevity. The section on subarachnoid hæmorrhage is well done, and so is the description of the clinical evolution of disseminated sclerosis.

Art and the Scientist

GEOFFREY LAPAGE, M.SC., M.D., late lecturer in animal pathology, University of Cambridge. Bristol: John Wright. 1961. Pp. 115. 42*s*.

SECTION IV begins: " Although this book is concerned chiefly with scientific illustration done by scientists who belong to Groups B(1) and C defined previously, it will be useful to glance briefly at some illustrations that belong to Groups A and B(1)—namely . . . " The passage is quoted not to deter but to warn prospective readers. So conditioned are we to think of art and science as elements apart that their coupling in the title might suggest something faintly whimsical—a cultivated form of late-night entertainment rather than a learned treatise. But perhaps scientific illustration—an unjustly neglected art-form—does call for a scientific rather than a literary or purely æsthetic approach. Much of the text is devoted to a general discussion of the kinship between artistic and scientific creation; and the author —like so many great men before him—has found it hard to illuminate this difficult subject. In the historical review, the width of Dr. Lapage's sweep is too great to present in detail any one style, period, technique, or branch of science. Instead, he gives us scholarly snippets of information—some fascinating—from which no general picture emerges.

Four of the illustrations are in colour and all are beautifully reproduced; but Hooker's fine *Jacobean Lily*, Gosse's drawings of a mouse, Dobell's *Intestinal Amœbæ*, Scarpa's flamboyantly baroque dissection model, and sketches from E. A. Wilson's *Antarctic Diary* have little in common, apart from their general interest and differing artistic merit. Two splendid representations of the human skeleton—one by Vandelaar from Albinus's famous *Tabulæ Sceleti* (1747) and the other by Cheselden—as well as some interesting information scattered in the text may make medical readers regret that the author did not restrict himself to the little-known and now almost extinct art of anatomical illustration.

A Textbook of Clinical Pathology

6th ed. Editor: SEWARD E. MILLER, M.D., professor of internal medicine and industrial health, University of Michigan, Ann Arbor, Michigan. London: Baillière, Tindall & Cox. 1960. Pp. 894. 120*s*.

A Syllabus of Laboratory Examinations in Clinical Diagnosis

Revised edition. Editors: LOT B. PAGE, M.D., assistant physician, PERRY J. CULVER, M.D., associate physician, Massachusetts General Hospital, Boston. Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1960. Pp. 580. 60*s*.

Two large volumes on a specialty which is in its early days in this country—one in its second, the other in its sixth edition. They are not cookery books (which are familiar enough), written for pathologists or laboratory technicians; nor are they clinical texts with a mild laboratory bias. They represent a comparatively new and characteristically American approach to medicine—the nearest thing we have to what might fairly be described as " clinical science ". This is synonymous with " laboratory medicine " only in the sense that it is based on scientific experiment rather than clinical findings, on numerical data rather than subjective impressions, and on the exploitation of laboratory apparatus rather than the use of the unaided senses. The new science needs no advocacy: its advance is certain. Nor is it necessary to contrast the old and the new: it is common enough experience that doctors who walk about with little black boxes (which flash, buzz, and record), who can handle a test-tube, to whom standard deviation is more than a whiff of scientific jargon, and who can distinguish a polymorph from a lymphocyte under the microscope, are often better clinicians in the old as well as in the new sense than those who pride themselves on their clinical acumen to the exclusion of everything else. Still, it is perhaps too much to hope at this stage that either of these books will find its way into the hands of the British student or houseman (for whose American counterparts they are intended): the student is too preoccupied trying to divine the minds of mostly conservative examiners, the houseman is busy learning the practical tricks of his craft. What can be hoped, however, is that one of these books at least will become readily available in medical-school and hospital libraries for those to whom medicine means more than passing exams and applying traditional doctrines at the bedside.

Of the two volumes the *Syllabus* is the better. It deals with almost all branches of laboratory medicine (including good chapters on cardiac catheterisation and lung-function tests) with remarkable brevity. The chemical section (written by the editors) is especially lucid and well-informed; but all contributors have achieved an exceptional balance between theory and practice. It is true that many of the techniques, particularly the hæmatological ones, do not conform to standard British practice, but in some ways this adds to the interest of the book. Despite its many useful qualities, the *Textbook* is not always free from the vices which many associate with this genre, and some of the chapters have a weighty, almost legal, style. Half the price and two-thirds the length will clinch the preference of many for the *Syllabus*.

Evolution and Progress

Essays in Sociology and Social Philosophy. Vol. III. MORRIS GINSBERG. London: William Heinemann. 1961. Pp. 283. 25*s*.

THOSE interested in the theoretical background of social processes and social problems will enjoy this book. It is the third volume of Professor Ginsberg's collected papers, and is largely devoted to an assessment of the theory of evolution as applied to social change and to making out a case for the idea of progress.

The book is a collection of essays divided into two parts. Those in part I have already been published elsewhere. Professor Ginsberg argues that, despite the attacks which have been made on it, and the fact that so far no general law of progress has been established, the idea of progress nevertheless retains its vitality. Any theory of progress involves reference to ethical standards, and it is here that wide differences of opinion develop. One essay is devoted to a discussion of the works of L. T. Hobhouse, because Ginsberg, with Hobhouse, believes in the possibility of a rational ethic. By a rational ethic, he means an ethic that is based on a knowledge of human needs and potentialities and of the principles of justice. But knowledge alone will not suffice. The optimism of the early theories of progress which assumed that intellectual development was the chief or sole determinant of social progress is dead and beyond hope of resurrection. But knowledge is still the first essential. Having achieved it, the choice is ours.

The essays in part II have not been published before and are devoted to aspects of European sociology in the early twentieth century. They include some instructive reviews of the theories of some of the greatest sociologists of that period. There is another chapter devoted to evolution and progress. " Whatever progress has been made is certainly not automatic or assured, and a breakdown remains possible. Yet there is good ground for maintaining that modern societies have come to have deeper insight into the nature of social ideals and a firmer grasp of the conditions needed to attain them. To this extent there is reasonable justification for the belief in the reality of social progress."

The atmosphere of the book is hopeful and encouraging: it will have a special appeal to those who are optimistic at heart.

Developmental Genetics and Lethal Factors

ERNST HADORN, professor of zoology and comparative anatomy in the University of Zürich. Translated by URSULA MITTWOCH. London: Methuen. 1961. Pp. 355. 52*s*. 6*d*.

THE first half of this book could be regarded as a text on genetics, since lethal, as the author admits, are only arbitrarily separable from other mutants. The second half deals with the pathogenesis of the mutant phenotype and contains some interesting chapters on somatic segregation, transplantation experiments, phenocopies, biochemical aspects, and similar topics.

It is a pity that the original German edition of this book in 1955 was not accompanied at the time by an adequate English translation such as this one. The incorporation by Hadorn of over 60 references from the intervening years has partially succeeded in giving the appearance of a recent book, but naturally, in view of the rapid advances in genetics recently, most paragraphs would have been written differently today. Similarly, biochemical concepts and examples would have been more in evidence in all the twenty chapters instead of being confined largely to a single chapter. Hadorn himself has made striking advances in the biochemical as well as in most other facets of physiological genetics and the book, through its German edition, has almost the reputation of a classic. Relevant experimental data on a large number of mutants and their phenocopies in numerous species are brought together as in no other single source. As a reference book, therefore, and as a guide to teratological concepts, this translation can be recommended to all those concerned with this subject, provided that they do not mind the zoological rather than the anthropocentric approach. Here is one zoologist who does not pretend to know medicine, and the medical reader must be prepared to notice that some of the points could have been better illustrated on the human species.

Exceptional Children

Residential Treatment of Emotionally Disturbed Boys at Shotton Hall. F. G. LENNHOFF. London: George Allen & Unwin. 1960. Pp. 183. 21*s*.

THE "exceptional children" are the pupils, past and present, of Shotton Hall, a community school, of which the author is the principal. It takes 35–40 boys aged 10–16 years, of good intelligence and potential ability, who are fundamentally capable of good adjustment, but who for many different reasons and because of various experiences cannot cope with the day-to-day demands of social integration and are consequently unhappy, lonely, and bewildered. It is characteristic of the author's sympathy for these children that in his title he calls them "exceptional" rather than "maladjusted".

Considerable attention is given to the descriptions of the daily lives of the children, to their difficulties in learning, to their lives outside the classroom and to some of the problems they meet. The author might be described as "analytically orientated"; he obviously uses his psychiatric knowledge as a useful adjunct to his immense humanity and commonsense. He also has the unusual capacity of caring tremendously about children who are going through periods of exceptional maladjustment and whom most people would, therefore, find particularly unattractive.

In a foreword, Dr. Edward Glover says that the "school" that Mr. Lennhoff has built up "combines the functions of informal education with those of a psychological first-aid post, a child guidance unit, a treatment centre, a psychic convalescent home and a psychological laboratory in which pathological processes can be studied in vivo and the most desirable modes of normal upbringing inferred and tested". He suggests that by establishing throughout the country a sufficiency of schools on the Shotton-Hall model we might reduce the population which, left to its own unaided devices, may gravitate later to Wormwood Scrubs. It might be added that if there were more teachers like Mr. Lennhoff, not only in schools for maladjusted children, but also in ordinary schools, there would be fewer maladjusted children to start with.

Spiritual Therapy

How the physician, psychiatrist, and minister collaborate in healing. RICHARD K. YOUNG, ALBERT L. MEIBURG. London: Hodder & Stoughton. 1961. Pp. 179. 15*s*.

"IN this book two pastors tell the story—in case-history form—of their ministry of healing in one of the world's most modern hospitals." The hospital is the North Carolina Baptist Hospital, where the first author directs a "school of pastoral care" and where, working in close association with physician, surgeon, and psychiatrist, the chaplain is an accepted member of the therapeutic team. The book is primarily one of instruction and advice to student pastors and hospital chaplains on giving pastoral aid to inpatients and outpatients, especially those with psychosomatic disorders, mothers giving birth, those who are to have an operation, women in the menopause, bereaved relatives, but, perhaps significantly, not the dying. Restoration of bodily health and relief of suffering rather than the healing of sick souls is the object.

Constitutional factors in disorders of function are perhaps underestimated and particular emotional conflicts may be too readily correlated with particular clinical pictures; but claims are not pitched too high and the advice is sound. Granted that the "personal doctor" is not, or has no time to be, concerned with the spirit, that the psychiatrist's territory is deep analysis, and that the patient will accept "pastoral counselling", there is much to be said for the medico-pastoral team. There is most certainly a place for it, though perhaps a more confined place in this country than in the United States. A laudatory introduction by the editor of *The Reader's Digest* and a statistical analysis of the familiar reactions to bereavement may seem misplaced; but the book contributes something towards meeting a challenge with which doctors are being openly and increasingly confronted.

Protein Biosynthesis (London: Academic Press. 1961. Pp. 409. 95*s*.).—The synthesis of proteins has long been recognised to be a cellular function required for growth, replacement of wear and tear, and secretion, but more recently the fragmentation of cells into structural subunits, such as the mitochondria and ribosomes, has enabled aspects of these processes to be functionally isolated and studied apart. This book, edited by Dr. R. J. C. Harris, is the record of an international conference of men and women working on this subject, at which 26 papers were read and discussed. The subjects included the synthesis of glutathione, the transport of amino-acids into the subcellular structures and their "activation" there before being incorporated, protein synthesis on myofibrils, and other allied problems. In short, the conference dealt with many aspects of cellular activity, and some of the articles demand a background knowledge to appreciate them to the full. But books like this have a value for the less specialised reader who wishes to keep up with current thought. He may not understand every word but he should be able to get at the general principles and he will need them, for this kind of biochemistry has come to stay. The study of protein biosynthesis is likely to have a great impact on physiology, pathology, and medicine.

Thrombosis and Anticoagulant Therapy (Edinburgh: E. & S. Livingstone. 1961. Pp. 98. 17*s*. 6*d*.).—If proceedings of conferences or courses are to be published at all, they should appear as soon as possible and should be inexpensive. This account, edited by Dr. William Walker, of a symposium held last September in Dundee meets both these points and provides a record of views and discussions on many subjects of current controversy: for example, the choice of tests for controlling anticoagulant treatment, the factors influencing the formation of thrombi, and complications that have arisen with blood used in extracorporeal circulation systems. These proceedings are well worth reading.

THE LANCET

LONDON 8 JULY 1961

Insulin

THE more we learn about insulin the less we understand it. It was the first protein-type molecule to have its aminoacid structure fully elucidated, and its physicochemical properties have been more precisely defined than those of any other peptide hormone. Vast clinical series and the cumulative experience of thousands of physicians have established its scope and limitations as a therapeutic agent. Its remote physiological effects both on the intact organism and on isolated organs have been studied in minute detail. And yet, because we still cannot relate our chemical data to our physiological findings and either to our clinical experience, we are hardly nearer than were the first workers on insulin forty years ago to answering the crucial questions: What does insulin do and how does it do it? But perhaps the stage is at last set, even if the action is yet to begin.

In view of the formidable potency of insulin (and the hard work that has gone into unravelling its structure), its formula, revealed by the patient studies of SANGER and his associates,[1 2] seems extraordinarily humdrum. The fifty aminoacids which make up its two peptide chains (conventionally labelled chain A and B) are in no way unusual; nor, at first sight, is their configuration very different from the aminoacid sequences of other proteins. Some of the aminoacid residues are, in fact, dispensable for physiological activity; indeed, whole chunks of chain B can be split off by proteolytic enzymes without impairing the potency of the rest. Other units seem to be freely interchangeable and vary among insulins extracted from different species: they seem to have no function other than to fill the gap between a few essential groupings. Perhaps the most remarkable feature of the molecule is its sulphur-containing aminoacid units and particularly the -S-S- bridges of the two cystine ($COOH\text{-}CHNH_2\text{-}CH_2\text{-}S\text{-}S\text{-}CH_2\text{-}CHNH_2\text{-}COOH$) residues which connect the peptide chains. (A third cystine residue forms an integral part of chain B.) Not that such intramolecular -S-S- bridges are in themselves peculiar to insulin: similar linkages occur in most polypeptides. What gives them special significance is that their disruption (either by oxidation or reduction) deprives insulin of all physiological activity.[3 4]

As free aminoacids or as subunits of larger molecules cystine and cysteine are readily interconvertible. Under suitable conditions any reducing agent can split the -S-S- bond of cystine and create two free -SH (thiol) groups; and two cysteine molecules readily give up their hydrogen atoms to suitable hydrogen acceptors to reunite as cystine under the catalytic influence of metal ions. These twin reactions occupy a central place in cellular metabolism and especially in tissue respiration. To those who derive neither intellectual nor æsthetic pleasure from chemical formulæ this process must seem the most extravagant of biochemical fantasies. Essentially it involves the provision of energy through the catalysed transfer of hydrogen ions from primary substrates either to oxygen (as in aerobic respiration) or to a final hydrogen acceptor (as in anaerobic respiration or fermentation); but this transfer is hardly ever accomplished directly. Instead, the hydrogen ions are passed down a long line of intermediate carriers in a complex system of chain reactions (a reflection, perhaps, of millions of years of chemical apprenticeship before Nature acquired the knack of oxidation by molecular oxygen). To several of these dynamic transformations the alternate hydrogenation and rehydrogenation of -S-S- bonds adds an essential link. Glutathione, two tripeptides united by an -S-S- bridge, acts as the hydrogen acceptor to many intracellular dehydrogenases [5 6]; and a host of other key enzymes not directly concerned with dehydrogenation require the presence of free thiol groups. Lipoic acid, an 8-carbon compound with an -S-S- linkage between the 6th and 8th carbon atom, combines with the anaerobic end-products of both fat and carbohydrate metabolism and launches them on their aerobic metabolic pathway. Coenzyme I, a primary hydrogen carrier in the final phases of tissue respiration, depends for activity on the coupled reduction of -S-S- bonds. With its three easily reduced cystine residues insulin might be thought to be yet another hydrogen carrier (and provider of thiol groups), were it not that the breakup of its disulphide links is apparently irreversible and entails permanent inactivation. Nevertheless many workers still believe that insulin may be in some way involved in thiol metabolism.

Reviewing some of the current hypotheses of insulin action, RANDLE and YOUNG have recalled that the transport of sugars into muscles is depressed by poisons which are known to block -SH groups [7 8]; and, though this block requires rather unphysiological conditions, sugars and perhaps aminoacids traversing cell membranes may conceivably enter into combination with -SH proteins. Moreover, these -SH proteins may possibly be maintained in a reduced (i.e., reactive) state by reduced coenzyme I; and cells may make reduced coenzyme available by operating an insulin-dependent " redox pump ". (The concept of a " redox pump " was applied by CONWAY [9] to gastric hydrochloric-acid secretion: he pictured a mechanism whereby

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2. Sanger, F. *Brit. med. Bull.* 1960, **16**, 183.
3. Lens, J., Neutelings, J. *Biochem. biophys. Acta.* 1950, **4**, 501.
4. Stern, K. G., White, A. *J. biol. Chem.* 1937, **117**, 95.
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6. Scheuch, D., Kahrig, C., Ockel, E., Wagenkecht, C., Rapoport, S. M. *Nature, Lond.* 1961, **190**, 631.
7. Battaglia, F. C., Randle, P. J. *ibid.* 1959, **184**, 1713.
8. Randle, P. J., Young, F. G. *Brit. med. Bull.* 1960, **16**, 237.
9. Conway, E. J. Biochemistry of Gastric Secretion. Springfield, Ill., 1953.

actively secreting cells continually de-electronated and ejected hydrogen ions while abstracting cations from plasma.) There being nothing obviously *recherché* about the structure of insulin, its metabolic effects seem all the more varied and impressive. Everyday experience conditions us to think of it simply in terms of fat and carbohydrate utilisation, but it probably plays a no less important part in the transport of aminoacid and the maintenance of protein cell-structure. If a common mechanism underlies these diverse actions, this may involve tissue respiration and the provision of free energy, possibly with control over the supply of reduced coenzyme. While such hypotheses are purely speculative, good clinical evidence points to the association of certain types of diabetes with disturbances of thiol metabolism. Dimercaprol (BAL) (which owes its protective function against war-gas poisoning to its two thiol groups) has been shown to benefit some cases of post-traumatic and severe insulin-resistant diabetes [10]; and, though its primary point of action (like that of insulin) remains obscure, its ability to compete with thiol-immobilisers almost certainly accounts for its hypoglycæmic effect. Sulphydril substances also play a part in the metabolism of insulin itself; and they provide at least a theoretical link between the action of insulin and some oral hypoglycæmic compounds. For some years now, two distinct tissue pathways of insulin breakdown have been recognised: first, a series of heat-labile reactions which probably depend on the action of proteolytic enzymes (the so-called "insulinases") [11–13]; and second, the break-up of cystine bonds by heat-stable reducing agents. The action of one, reduced glutathione (G-SH), has been diagrammatically represented by WILLIAMS [14]:

$$\text{Insulin} + 2\ \text{G-SH} \xrightarrow{\text{dialysed liver enzyme}} \text{reduced insulin} + \text{GS-SG}.$$

Several workers have shown that tolbutamide (and to a far lesser extent insulin) raises the serum level of G-SH [15–17]; and perfusion experiments by GRYGLEWSKI and DUNCAN [18] suggest that the tolbutamide-induced depression of hepatic glucose release noted by KÁLDOR and POGÁTSA [19] may be associated with reduction of G-SH concentration in liver cells.

The difficulties of piecing together such fascinating fragments of information arise from our inability to measure insulin activity either in vitro or in some simple biological system. None of the present assay methods (of which glucose uptake by rat diaphragms is perhaps the most popular) are either reproducible or sensitive enough; and all have the disadvantage of relying on what are probably only remote metabolic effects. A major break-through in experimental methods is needed before we can hope to advance our basic understanding of what insulin actually does.

10. Butterfield, W. J. H. *in* Symposium on the Mechanism of Action of Insulin. Oxford, 1960.
11. Lehmann, H., Schlossmann, H. *J. Physiol.* 1939, **94**, 15.
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13. Kenny, A. J. *Brit. med. Bull.* 1960, **16**, 202.
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15. Lazarow, A. *in* Symposium on Glutathione (edited by S. P. Colowick). New York, 1954.
16. Butturini, V. *G. Med.* 1956, **37**, 1217.
17. Duncan, L. J. P., Baird, J. D. *Pharmacol. Rev.* 1960, **12**, 91.
18. Gryglewski, R., Duncan, L. J. P. *Quart. J. exp. Physiol.* 1961, **46**, 150.
19. Káldor, A., Pogátsa, G. *Lancet*, 1960, ii, 439.

Hospitals for the Aged

THE immediate reaction on reading Dr. J. H. SHELDON's report [1] to the Birmingham Regional Hospital Board on its geriatric services must be one of horror at the descriptions of hospitals for the aged sick. Commenting on some of the hospital slums, he states:

> "By and large they do no more than provide storage space for patients under conditions of considerable difficulty, and often unpleasantness for the nursing staff. It was quite an experience to see bed pans stored for the night in the bath; to be told of female nurses having to queue up for the same lavatory as the male patients; to find the same room being used for the washing of bed pans and domestic crockery; and to see nurses having to fill a pint pot with water in order to wash excreta from a bed pan down an ordinary lavatory."

In his graphic descriptions Dr. SHELDON does not imply blame or criticism since these defective buildings, inherited by the health service in 1948, expressed the social conscience at the times they were built—in one case nearly eight hundred years ago. Some hospital management committees have tried strenuously to improve the conditions in the old-fashioned structures, but the sheer magnitude of the task has limited achievement. Many of the buildings served quite well their original purpose—namely, the care of the bed-fast chronic sick. But the facilities provided are quite inadequate for modern practice. In some cases modernisation is possible, but in others the design is so completely inappropriate that demolition and replacement is the only reasonable solution.

In his introduction Dr. SHELDON gives clear warning of the growing pressure on the hospital service brought about by the relative increase in the number of the very old (over 75) within the total increase in the number of people of pensionable age. This group makes a disproportionate demand on the hospital services on account both of their general frailty and their disabilities resulting from degenerative diseases, and of their family and social circumstances. Already the pressure on the hospital service gives cause for anxiety. Unless this situation is accepted as "a major challenge of the immediate future this same pressure will end by silting up much of the hospital accommodation for acute cases which up to the present has captured the major enthusiasm for hospital expenditure".

Ten hospital groups in the Birmingham region have specialist geriatric physicians, and their appointment is held to have been amply justified. Besides clinical responsibilities their work involves a considerable amount of social medicine, and they are required to integrate the hospital facilities with the various domiciliary and welfare services in the community. Although most geriatric units in the country have evolved from former "chronic sick" hospitals, it is not sufficient to redesignate such accommodation as a geriatric unit on the appointment of a specialist physician in geriatrics. The appointment should carry with it the obligation on the part of the board to provide money for the full facilities of an effective geriatric service. This obligation

1. Sheldon, J. H. Report to the Birmingham Regional Hospital Board on its Geriatric Services, 1961.

is seldom fulfilled. The report gives clear evidence of the lack of junior medical and ancillary staff in the hospitals concerned. As for capital expenditure, in the Birmingham region since the inception of the health service, only a sixteenth of the total has been devoted to beds for the chronic sick although these represent a seventh of the total number of beds in the region.

Dr. SHELDON pays just tribute to the devotion of the nursing staff to the patients. The hospital service in particular and society in general owe much to the part-time married nurse, and SHELDON comments on the outstanding impression, after visiting the chronic-sick hospitals in the region, of the contrast between the happy state of the patients and the deplorable conditions under which, in some places, the nurses have to work. The development of an effective geriatric unit depends largely on the work of the nurses, who should be given the best possible environment. The grossly inadequate conditions in the old chronic-sick hospitals with their overcrowded wards, out-of-date sanitary annexes, and lack of space for reablement and for equipment and labour-saving devices are in no way conducive to the recruitment of staff. Thus a vicious circle is established: the ward sister with insufficient nursing assistance is unable to maintain proper standards, and, under the burden of a mounting number of incontinent and sometimes neglected patients, nursing duties in the ward become increasingly unpopular.

It has been suggested that 1·2 geriatric beds per 1000 population will suffice [2]; but this takes little account of future trends, and particularly the problems posed by psychiatric illness in old age: the Mental Health Act of 1959 will increase the need for geriatric beds in general hospitals. Moreover, the accommodation provided by hospitals and by local authorities cannot be considered in isolation one from the other; and Dr. SHELDON suggests, as more realistic, a total of 3 beds per 1000 population. Although in the Birmingham region the expenditure on the geriatric service has been below the national average, the deplorable conditions and deficiencies described in the report are by no means confined to that region; and scrutiny of the hospital care of the aged sick in other areas would be timely, and perhaps no less disturbing. Meanwhile from Birmingham itself has come a proposal for a balanced hospital community [3] with a new approach to the care of the mentally ill and the aged sick.

2. Survey of Services Available to the Chronic Sick and Elderly 1954–55. H.M. Stationery Office, 1957.
3. McKeown, T., Mackintosh, J. M., Lowe, C. R. *Lancet*, 1961, i, 818.

Annotations

CHRONIC PYELONEPHRITIS

SINCE it was realised that chronic pyelonephritis is being detected much more often at necropsy than in life, efforts to diagnose this disorder [1 2] and to define its development from the acute phase [2 3] have been intensified. Undoubtedly the increased awareness among clinicians has benefited many patients with this condition. But this very awareness may cause the diagnosis to be made too often; for the clinical syndrome is indefinite, the necessary laboratory tests are not always readily secured, and it is all too easy to diagnose chronic pyelonephritis incorrectly when a patient's condition is improved by a therapeutic test.

Many different laboratory tests have been advocated. Thus Brod [4] (whose findings were largely confirmed by Gomori and Szendei [5]) showed that straight culture of the urine was positive in only 81% of cases, and that white cells in the urine were increased in only 76%. He noted that the loss of renal tubular concentrating power was quite out of proportion to the impairment of glomerular filtration-rate; but Kleeman et al.[6] found no glomerulotubular imbalance when the final stages of chronic renal failure were reached. Kass [7] and Sanford [8] advocated quantitative examination of a mid-stream specimen of urine from male and female patients; but even this is not fully reliable. Hutt et al.[9] used a battery of tests in investigating a series of cases of pyelonephritis and controls, and found that a bacterial pyrogen test [10] was very helpful both in diagnosis and in controlling the effect of treatment: this test is regarded as positive when the white-cell excretion-rate [11] (which in chronic pyelonephritis is often raised above the normal of 200,000 to 400,000 per hour) is increased by more than 100% and reaches more than 400,000 per hour following injection of a purified lipopolysaccharide obtained from *Salmonella abortus equi*. Few doctors can expect a full bacteriological and pathological examination of renal biopsy specimens, by means of which Kark et al.[12] showed that in some cases there was a typical pyelonephritic histological picture while in others there was a proliferative glomerulonephritis ("subacute bacterial nephritis") which under antibiotic treatment subsided with little fibrosis.

Clearly in any scientific assessment of chronic pyelonephritis the diagnostic methods must be rigorous and must be stated explicitly. Kimmelstiel et al.[13] conclude that an active pleomorphic inflammatory cellular infiltration of the kidney, particularly with polymorphs, is the most reliable criterion for the diagnosis of chronic pyelonephritis: in the absence of active exacerbation, the diagnosis can be made only by inference, and then only if, for each of the other criteria given, causes other than pyelonephritis are eliminated. The most suggestive of these criteria is the presence of thyroid-like areas; but such areas should not be regarded as suggestive of chronic pyelonephritis if they are near expanding lesions such as cysts or tumours, or near the corticomedullary junction (where Kimmelstiel et al. are convinced they are ischæmic in origin), and they must not be congenital. It seems very doubtful whether chronic pyelonephritis can be diagnosed on the basis

1. *Lancet*, 1956, i, 1000.
2. *ibid.* 1959, i, 1265.
3. *ibid.* 1956, ii, 1036.
4. Brod, J. *ibid.* 1956, i, 973.
5. Gomori, P., Szendei, A. *Acta med. hung.* 1958, **12**, 329.
6. Kleeman, C. R., Hewitt, W. L., Guze, L. B. *Medicine, Baltimore*, 1960, **39**, 3.
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8. Sanford, J. P. *J. Amer. med. Ass.* 1959, **169**, 1711.
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10. Pears, M. A., Houghton, B. J. *ibid.* 1959, ii, 1167.
11. Houghton, B. J., Pears, M. A. *Brit. med. J.* 1957, i, 622.
12. Kark, R. M., Muehrcke, R. C., Pirani, C. L., Pollak, V. E. *Ann. intern. Med.* 1955, **43**, 807.
13. Kimmelstiel, P., Kim, O. J., Beres, J. A., Wellmann, K. *Amer. J. Med.* 1961, **30**, 589.

of this appearance[14] without some other clinical or bacteriological confirmation. Glomerular changes are of limited value in distinguishing pyelonephritis from ischæmia: the very irregular distribution of lesions in pyelonephritis may be very helpful in distinguishing this from ischæmia at necropsy but not in biopsy material. Vascular changes are usually unhelpful, since those in pyelonephritis are mostly the same as those in renal arteriosclerosis and hypertension; only very rarely is true inflammatory arteritis found. Even the characteristic irregularity of distribution of the lesions in chronic pyelonephritis and the resulting cortical scarring may resemble changes due to ischæmia without pyelonephritis.

Applying these criteria very strictly to their own material over a six-year period, Kimmelstiel and his colleagues are prepared to halve their diagnoses of chronic pyelonephritis on necropsy specimens; and they claim that the incidence of the condition is not increasing and is certainly less than some have lately claimed. But they do not state how many of their cases were diagnosed during life, nor do any of their findings discount the occurrence of inapparent or subclinical pyelonephritis. In view of the finding of Kark et al.[12] that the histological changes may sometimes subside, the incidence of chronic pyelonephritis cannot be estimated from necropsy findings alone.

THE INFLUENZA VIRUS

LIKE an amœba, virology is pushing out in all directions; and new facts of fundamental biological importance have been revealed. For example, bacterial viruses are being intensively studied because they are suitable systems for the investigation of the elementary and fundamental processes of gene action. Brenner et al.[15] have labelled cells with heavy carbon and nitrogen and separated by centrifugation the ribosome nucleic acid particles of cells producing bacteriophage. Evidence thus collected suggests that special "messenger" molecules carry information from the desoxyribosenucleic acid of the gene to the ribosomes where specific proteins are synthesised.

In quite different studies, of equal interest, electron-microscopy and chemical analysis have told us a great deal about the structure of influenza and similar viruses. They apparently have a membranous outer "skin" with a complex structure containing hæmagglutinin, antigen, enzyme, and lipid components.[16 17] Inside the particle is coiled a long spiral structure which is probably a ribonucleoprotein carrying the soluble antigen activity and the genetic information. The aminoacid composition of the protein of various parts has been determined after fragmenting the particle by ether treatment.[18]

Modern chemical and physical methods do not seem to have been applied so much to the study of the effect of virus infection on the patient or the whole animal. By means of fluorescent-antibody methods, Hers and Mulder[19] have identified virus-infected alveolar cells in the lungs of patients who had died of influenza-virus pneumonia. (Without a specific method for identifying virus-infected cells it had always been possible to argue about how much of the pathological changes represented the direct effect of virus multiplication in lung cells.) Louria et al.[20] showed that in such cases there was, during life, a reduced blood-oxygen and increased blood-carbon-dioxide with decreased blood-pH. By means of digital plethysmography Burch et al.[21] demonstrated constriction of the peripheral blood-vessels in non-fatal cases of influenza. More physiological measurements would probably reveal further facts about the bodily responses to this and other virus infections. The gap between our knowledge of influenza pathology and of the generalised febrile and toxic reaction is as great as that between our knowledge of the structure of influenza-virus particles and the new ideas on ribosome "messengers".

YOGA

THE ancient Yoga takes many forms, in which physical and mental doctrines are followed separately and together. Yogis have claimed ability to control certain involuntary bodily functions, to survive live burial, and to control heart-beat.

Survival after live burial implies voluntary control over metabolic activity and oxygen consumption. Shri Ramanand Yogi, of Andhra, claimed to have been sealed in a dugout underground pit for 28 days. Anand et al.[22 23] enclosed him in an airtight metallic and glass box, with an effective capacity of 2263 litres, for 8 hours on one occasion and 10 hours on another. Two other individuals were studied as controls; one stayed in the box for 4 hours and the other for 7 hours.

The basal oxygen utilisation of Shri Ramanand, determined with a Benedict-Roth B.M.R. apparatus, was calculated to be 19·5 litres per hour, which was within the normal range for his surface-area. During his 8-hour confinement an average of 26·9 litres per hour was used in the first 3 hours, while a candle was burning in the box, and 12·2 litres per hour after the candle went out. In the second experiment the oxygen consumption averaged 13·5 litres per hour—21·3 litres in the first hour and 10 litres per hour in the middle part of the experiment; his carbon-dioxide output followed the oxygen uptake reciprocally. One control showed no change in basal oxygen requirement in each of two 4-hour experiments, while the other control showed an oxygen consumption above basal requirement in the 7-hour experiment. Respiratory and cardiac rates increased in both controls as the oxygen concentration fell and the carbon-dioxide concentration rose. Shri Ramanand, on the other hand, had an initial heart-rate of 85 per minute, and in the greater part of the experiment it ranged between 60 and 72 even though the oxygen concentration fell from 19·33 to 15·86%. In the last hour, when the oxygen concentration fell from 15·86 to 14·64%, the pulse-rate rose to 80–90. Simultaneously, the carbon-dioxide concentration rose from 1 to 5% and then, at the end of the last hour, to 5·6%. Meanwhile, his respiratory rate remained at 20 per minute during the first 8 hours and rose to 26 in the last 2 hours. An electroencephalogram during the experiment showed low-voltage fast activity and other changes

14. Jackson, G. G., Poirier, K. P., Grieble, H. G. *Ann. intern. Med.* 1957, **47**, 1165.
15. Brenner, S., Jacob, F., Meselson, M. *Nature, Lond.* 1961, **190**, 576. See *Lancet*, 1961, i, 1333.
16. Horne, R. W., Waterson, A. P., Wildy, P., Farnham, A. E. *Virology*, 1960, **11**, 79.
17. Horne, R. W., Waterson, A. P. *J. mol. Biol.* 1960, **2**, 75.
18. Hoyle, L., Davies, S. P. *Virology*, 1961, **13**, 53.
19. Hers, J. F. Ph., Mulder, J. *Amer. Rev. resp. Dis.* 1961, **83**, 84.
20. Louria, D. B., Blumenfeld, H. L., Ellis, J. T., Kilbourne, E. D., Rogers, D. E. *J. clin. Invest.* 1959, **38**, 213.
21. Burch, G. E., Walsh, J. J., Mogabgab, W. *Amer. Rev. resp. Dis.* 1959, **79**, 68.
22. Anand, B. K., Chhina, G. S., Singh, B. *Indian J. med. Res.* 1961, **49**, 82.
23. Anand, B. K., Chhina, G. S. *ibid.* p. 90.

associated with the drowsy state of sleep replacing the basal dominant alpha rhythm. Delta rhythm, associated with deep sleep, was not recorded. Two or three hours after the end of the experiment Shri Ramanand developed a pyrexia of 101·5°F, which lasted 6–7 hours. He stated that this happened after each live burial.

Anand et al. interpret these results as indicating a voluntary reduction of basal metabolism, possibly mediated through the autonomic nervous system, which this man could induce by his Yogic practices.

Three Yogi who claimed to be able to stop their hearts beating were studied during several attempts, each lasting 10–20 seconds.[23] At each attempt the subjects voluntarily increased their intrathoracic pressure by holding their breath in inspiration and expiration with a closed glottis and forcibly contracting the abdominal and chest muscles. Anand and Chhina found that heart-sounds became inaudible to auscultation and that pulsation in the radial artery and in a finger plethysmograph disappeared during these attempts, but no electrocardiographic or radiographic arrest of the heart was demonstrable.

STICKINESS OF PLATELETS

THAT blood-platelets adhere to and agglutinate on rough or foreign surfaces has been known since they were originally described by Bizzozero in 1882. When a small blood-vessel is injured, platelets adhere almost at once to the damaged tissue and soon a plug of platelets is built up which seals off the bleeding-point. Platelets are also liable to adhere to foreign surfaces, especially glass. Payling Wright [1] showed that, when blood mixed with the usual anticoagulants was rotated in glass vessels, the platelet-count fell rapidly and the missing platelets could be found sticking to the glass walls. These two observations have recently been used in devising methods for measuring platelet "adhesiveness" in vivo and in vitro.

Borchgrevink [2] thought that, if platelets adhere to the cut surface of vessels, the blood issuing from a wound should have a lower platelet-count than normal blood. He specified a standard cut in the skin of the forearm to represent the wound and used venous blood as the normal standard. In fifty observations about 37% of the total number of platelets remained in the wound, presumably adhering to the damaged surfaces. Heparin made no difference to this sticking of platelets in the wound; even when the clotting-time of the blood was 6 hours, there was the same difference between the platelet-counts of wound blood and normal blood.

O'Brien [3] has also described ingenious techniques for studying platelet adhesiveness. He has a special apparatus for measuring adhesiveness to glass; and for measuring adhesiveness to damaged cells he mounted sheets of human amnion cells on glass and "damaged" them by heating to 56°C for 30 minutes. He found that where blood was trickled over undamaged cells, no platelets adhered although they could be found sticking to the glass in many areas not covered by cells. But when blood was similarly trickled for 15 seconds—i.e., before any fibrin could form—over damaged cells, many platelets stuck to the cell surfaces. By these techniques he has confirmed that heparin does not affect platelet adhesiveness either to damaged cells or to glass. He also examined platelets from patients who were being treated with the anticoagulant phenindione, and found that adhesiveness to glass was unaltered. In blood from patients with some coagulation disorders—hæmophilia, Christmas disease, Hageman trait, and congenital afibrinogenæmia—platelet adhesiveness was unaltered. Similar results from a larger series of patients with coagulation defects were reported by Hellem.[4] In addition, O'Brien has investigated the anti-adhesive properties of some twenty drugs. Drugs that prevent adhesion of platelets to damaged amnion cells and to glass include salicylates, procaine, and some antihistamine drugs. These antiadhesive drugs may prevent the adhesion of platelets to a cut capillary, and O'Brien believes that they might prevent the formation of a thrombus: he has previously suggested that the adhesion of a few platelets to a local area of damaged arterial wall is almost certainly an essential step in thrombus formation.[5] Unfortunately the concentrations at which these drugs are effective are all dangerous, but a drug that would be effective in non-toxic concentration may be found now that methods of testing have been devised.

These techniques for estimating platelet adhesiveness may also help us to define the ætiology of some more of the obscure cases of hæmorrhagic diathesis that do not fall into any of the recognised groups. One such is Glanzmann's "thromboasthenia", in which the bleeding-time is prolonged and clot retraction is poor but the platelet-count is normal and all the usual clotting factors and thromboplastin generation are normal. Borchgrevink [2] has investigated a case of this type, in a boy of 18 who had already been in hospital about fifty times on account of epistaxis and gastrointestinal bleeding. When the "standard wound" test was applied, there was no difference between the venous platelet-count and the wound blood-count, suggesting that platelets had not adhered to the cut vessels. This patient's platelets also showed no viscious metamorphosis in the presence of thrombin.

STRESS INCONTINENCE

THE preservation of urinary continence is commonly related to the combined efforts of the internal and external urinary sphincters, without regard for the part played by the intermediate portion of the urethra. Such a view is untenable since wide resection of the bladder neck is compatible with full control and passive continence is retained when the external sphincter is deliberately paralysed by pudendal block or neurectomy. This was clearly shown by Caine and Edwards,[6] whose cineradiographic studies in prostatectomised patients also demonstrated the importance of preserving the integrity of the short segment of the urethra between the apex of the gland and the membranous sphincter. Thus urethral tonus, by passively resisting the outflow of urine from the bladder, is apparently of distinct value in maintaining continence at rest; and when the urethra becomes weakened or dilated as the result of obstetrical trauma it becomes unable to resist the strain of sudden increases in vesical tension resulting from coughing or straining.

This incapacity may be modified according to Enhörning,[7] who suggests that any rise in intraperitoneal

1. Wright, H. P. *J. Path. Bact.* 1941, **53**, 255.
2. Borchgrevink, C. F. *Acta med. scand.* 1960, **168**, 157.
3. O'Brien, J. R. *J. clin. Path.* 1961, **14**, 140.
4. Hellem, A. J. *Scand. J. clin. Lab. Invest.* 1960, **12**, suppl. 51.
5. O'Brien, J. R. *Postgrad. med. J.* 1960, **36**, 558.
6. Caine, M., Edwards, D. *Brit. J. Urol.* 1958, **30**, 34.
7. Enhörning, G. *Acta. chir. scand.* 1961, suppl. 276.

pressure is uniformly transmitted. Using a special double catheter connected to traducers which were capable of measuring minute rapid variations in tension, he was able to demonstrate simultaneous and comparable increases in vesical and urethral pressure in healthy subjects during coughing. Furthermore it seemed that the increase of pressure was greatest in the proximal part of the urethra lying above the pelvic floor. While in health the intra-urethral pressure always exceeded that in the bladder, in patients with stress incontinence this difference was reduced and during straining became reversed. This was attributed to deficient transmission of intraperitoneal pressure to the intrapelvic urethra owing to structural weakness or widening of the urethra, or alternatively to the reduced power of the tissues in the anterior vaginal wall to counteract sharp rises in the intra-abdominal pressure. This implies that, if the urethra has become funnel-shaped or the pelvic floor weakened, any rise in intraperitoneal pressure produced by straining may be dissipated over a wider area. In this event urethral closure may become impaired and incontinence may ensue.

Despite the comprehensiveness of Enhörning's research and the apparent uniformity of his results, there are some grounds for criticism. In the first place the introduction of a catheter may itself affect urethral tonus. Similar investigations of the hydrodynamics of hydronephrosis have suffered from this defect, and Enhörning's report would have been more convincing had it been supported by cineradiographic evidence. Secondly, in the report the position of the bladder and any associated weakness of the pelvic floor are largely discounted. It seems quite possible that in certain circumstances reflex contraction of the pelvic floor may alter the course of the urethra and thus contribute to its closure. Nevertheless the care and precision with which the studies were undertaken merit detailed consideration even if the eventual conclusion is that " the beneficial effect of surgical treatment may be attributed chiefly to the reinforcement of these tissues so that the urethra is more readily exposed to increases in intra-abdominal pressure ".

THE GUESSING GAME

DOCTORS who battle daily with the microorganisms causing disease in the community will sometimes ruminate on the nature of the unseen machinery that engineers all this morbidity. Especially in the case of the common respiratory diseases, it is fascinating to speculate on what determines the timing of the disease in those who are attacked in household outbreaks, and why some escape. Unfortunately few of us have the time, the inclination, and the necessary mental equipment to frame the right questions in terms precise enough to evoke informative answers—unfortunately because our ignorance of the epidemic and endemic behaviour of these common diseases contrasts sharply with our more complete knowledge of such relatively rare conditions as the enteric fevers.

Medical statisticians have drawn attention to what may be called the dynamics of outbreaks of disease. Where so much is uncertain they too have to fill in lacunæ by guesswork, but they cast their guesses in a precise and quantitative form and incorporate them into a theoretical model of an epidemic which can be used for comparison with the pattern of an actual outbreak. If the theoretical predictions give a model that closely matches the conditions in the real epidemic, then it seems reasonable to suppose that the guesses have been good ones in the sense that they represent what is actually happening.

In earlier times this statistical approach was limited by the paucity of epidemic records. Without the discipline of actual checks, the theoretical models tended to proliferate unduly. The chief source of raw material lay in the notifications of infectious diseases, which are unsatisfactory in several ways. Lately investigations have provided reasonably precise observational data concerning household outbreaks of respiratory disease. Brimblecombe et al.[1] recorded the date of onset and the clinical nature of the upper-respiratory ailments in a group of families, similar in that each consisted of two parents and three children, but of varied social status. Now Heasman and Reid [2] have used this information to compare three different theoretical models, each of which makes a different assumption about the epidemic mechanism. The first model, due to Greenwood,[3] assumes that the infecting person is only briefly infectious and ignores the possible influence of more than one infecting person. Greenwood's model admirably predicted the generation of cases in the families subsequent to the introducing case, but was less successful in estimating the later generations of the outbreak. Reed and Frost [4] produced a similar model differing from that of Greenwood in assuming that the presence of more than one infecting person would produce a measurable effect. For the complete outbreak this hypothesis gave a better prediction than the Greenwood model. The third model, that of Bailey,[5] unlike the other two assumed that the infectious period had a definite duration with a gradual waning of infectiousness, and took account of the continuous mixing of infected and uninfected persons. Bailey's model gave a remarkably accurate prediction, especially for crowded households.

There are many sources of uncertainty in approaches of this type. The theoretical premises of the models are, by their tentative nature, insecure, and the field data subject to error. Brimblecombe et al. collected information fortnightly—a long interval for the fallible memory. A purely arbitrary minimum of ten days was allowed to elapse since the last case in the household before a new introduction of infection was deemed to have occurred. Recent work at Salisbury and elsewhere suggests that many varied viruses are continually circulating and are responsible for outbreaks of upper-respiratory disease, and each of these may be expected to have its peculiar behaviour. No account could have been taken of the possible effect of this state of affairs. Where so much was uncertain it is disconcerting that all three predictions were so accurate, and Heasman and Reid are wise in being slow to draw conclusions. They are, however, justified in claiming that " theoretical models of epidemic behaviour hold out prospects of fruitful application in the interpretation of data collected by field enquiry ". The prospect is indeed encouraging, and the call is for more field data in order that the theoretical models can be adequately tested against different epidemics in different areas, recorded by different people at different times.

1. Brimblecombe, F. S. W., Cruickshank, R., Masters, P. L., Reid, D. D., Stewart, G. T. *Brit. med. J.* 1958, i, 119.
2. Heasman, M. A., Reid, D. D. *Brit. J. prev. soc. Med.* 1961, **15**, 12.
3. Greenwood, M. *J. Hyg., Camb.* 1931, **31**, 336.
4. Reed, L. J. Frost, W. H. Cited by N. T. J. Bailey, The Mathematical Theory of Epidemics. London, 1957.
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Teaching of Everyday Psychiatry *

TEACHING OF PSYCHIATRY TO MEDICAL STUDENTS †

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To those who accuse medicine of becoming too scientific, I would answer that it has not become scientific enough. It has only just begun to use methods of scientific inquiry into areas of human experience previously dealt with and approached by intuitive and inspirational means. As I see them, the functions of medicine are to acquire knowledge, and to help man free himself both from the enslavement of pain and disease, and from the equal enslavement of morbid fear and guilt.

If medicine is to continue to meet these social and personal needs it must be informed and alert to changes, not only within itself, but also within its society. But this does not mean that it should be exclusively concerned with service, here and now, to the exclusion of other interests. The medical school, like all schools in the university, is a community of scholars, which should at all times provide the intellectual and emotional climate which will foster and encourage the critical pursuit of knowledge for its own sake as well as for its application to the prevention of illness and the care of the sick.

Today, in many Western countries, the doctor has an unusual opportunity to obtain a sound scientific training, to develop attitudes of critical perceptiveness, and to become informed. His basic medical education allows him to bring to the patient-physician relationship an attitude of affectionate and moral neutrality. Using his knowledge and skill, his insight and sympathetic understanding, his role is to study and help his patient but without becoming a censor or a judge. But if he is to deserve this position in society, and if he is to fulfil his responsibilities, he must have the preparation appropriate to his work. If he perpetuates the dichotomy of current belief and practice in medicine—if he tries to deal systematically and scientifically with the body but remains content to be intuitive and artistic in dealing with the mind and emotions—he will be found wanting.

How can the doctor of tomorrow become informed? How can he learn to behave more intelligently and work more effectively in understanding man, sick and well, in human terms?

THE TEACHING UNIT

In the United States during the past fifteen years, there has been a rapid increase in the number of psychiatric units in general hospitals, including some (though not all) university teaching hospitals. The psychiatrist is thus less isolated from the major theatres of medical teaching and research. In this new environment of the teaching hospital he has had to learn new methods quite different from those previously used in the sequestered mental hospital.

Medical-school departments of psychiatry have grown not only in number but in senior staff; in the area of clinical services for which they are responsible; and in the range of research interests and activities. With this growth has come an increase in the number and quality of candidates who seek to train as psychiatrists.

Though equally important work is done at a number of other centres, one may say that the principal places for psychiatric research and education are now the university departments, based increasingly in units within the university teaching general hospitals; and we believe that the increase in the number and quality of the candidates for career training in psychiatry is partly attributable to the physical presence and active membership of the psychiatric faculty in the teaching hospital. Through his teaching, his research, and his day-to-day work in all the clinical areas of the hospital, the psychiatrist serves as a model, among other models, in the medical faculty. Each student—according to his interest, aptitude, and motivation, and the opportunity afforded him—can search for and eventually establish his own identity from the various models presented by the faculty with which he is associated. This, we are sure, can be done consciously and intelligently without recourse to blind neurotic allegiance and its subsequent restrictions.

OBJECTIVES

What are our objectives in teaching of psychiatry to medical students? Is the teaching to be principally a preparation for those who will become psychiatrists? Is it to point especially to the family doctor of tomorrow—to the exclusion of the surgeon, the internist, the radiologist, and others? Neither of these has been, nor is, the primary purpose. Regardless of the eventual destinies of the students in the many fields of medicine, we try to meet certain needs they have in common.

First and foremost, we do all we can to encourage the student's curiosity and to foster his capacity for critical perceptiveness. By this we mean his need to question, to be sceptical, to subject data to his own inquiry, to examine the method and evidence of others—in short, for him to become critically informed.

Second is the need to understand the sequence of growth and decline in our society with attention to genic and experiential factors as determinants. In this he may learn about the emergence of man from early parasitic dependence to increasing capacities for interdependent human behaviour, and about the multiple-person field, the family, and other groups.

Third is the need to understand how the concepts of health and disease have developed from primitive animistic and more recent single-cause ideas to modern views of multiple causes and effects, of open rather than closed biological systems, of dynamic steady states rather than fixed immutable equilibria. In this we also draw attention to the frequent emotional crises in human family life, which by themselves do not constitute disease, but if neglected or mishandled may lead to disability.

Fourth is the need to understand the unique reciprocal relationships between patient and physician, and the latter's reciprocal relations with nurses, social workers, the clergy, health visitors, technicians, and others with whom he is associated in the care of the sick.

Fifth is the need to understand the psychology and sociology of the patient and his family in acute illness,

* A series of articles on the needs of students and practitioners, and how they may be met.

† From a University of London lecture delivered at the London Hospital Medical College on April 27, 1960; see *Lancet*, 1960, i, 1015.

chronic illness, convalescence, and disability; and the special problems of elective and urgent surgical intervention and of other episodes needing medical attention.

Sixth is the need to learn to recognise emotionally and mentally sick persons who express their distress in physical, psychological, or social symptoms. Traditionally this comes under the heading of psychopathology; but latterly there has been a tendency to extend it beyond classical descriptive psychopathology, in an attempt to learn more of the variations of normal development and behaviour—i.e., to learn more about the adaptive devices used at successive stages of life to meet the stresses, challenges, and rewards he may encounter. This implies reasonable mastery of methods of physical examination and of clinical psychiatric examination, and the judicious and critical use of accessory methods, such as physical and chemical tests and psychological examinations. It also implies the need to learn more about the zones of healthy and sick behaviour in our society, and the ability to distinguish between normal, neurotic, psychopathic, psychotic, and intellectually defective behaviour.

Seventh is the need, implied in the above, to learn how to listen to the patient's story and how to record it. The ability to interview properly is of the utmost importance in all branches of medical practice, and our teaching is directed to basic principles of interviewing patients, regardless of the nature of their presenting complaints. Implicit in the learning process is familiarity with the dynamics of the patient-physician relationship.

Eighth is the need for the doctor to understand what he can and should do:

1. In the management and treatment of emotionally healthy people who become sick.

2. In the management and treatment of the patient in whose family certain common emotional crises are being experienced.

3. In the management and treatment of emotionally sick patients who may or may not exhibit physical symptoms.

4. In the first-aid management of disturbed patients—the anxious and panicky, the delirious, the suicidal, the depressed, the grief-stricken, the excited, the aged, and the demented.

Ninth is the need for the doctor who is not a psychiatrist to understand what he cannot do and should not attempt. He must learn the limits of his own knowledge and skills, and how to make intelligent referrals to specialists, clinics, and hospitals. Here, too, he should learn the most effective ways of working with the psychiatrist and with the psychologist, social case-worker, nurse, occupational therapist, and others. He should be well informed, and capable of realistic appraisal of methods used in the treatment of the mentally sick.

Tenth, and last, is the need to know about the community resources which can be extensions of the doctor's care of his patient. The student should learn about the assistance to be obtained from social, welfare, and legal agencies and from the clergy, and about the existence and operations of special institutions for the chronically ill.

INTEGRATION

In the next article in this series Dr. Michael Kehoe will describe our department at the University of Rochester, New York, and its liaison with other parts of the medical school. From the beginning of the school, everything has been done to promote cooperation, because we are convinced that both the preclinical and the clinical departments profit by close association in their work. For this reason, separate institutes have been avoided: the aim has been rather to study and teach the problems of health and disease in such a way that students come to understand the bearing of all branches of medical science upon the particular problems with which they have to deal. To this end, the medical school and hospitals are united in a single large building of multiple wings and are under the same roof. My friend, the late Alan Gregg of the Rockefeller Foundation, once said to me: "You have the great advantage of being within bareheaded distance of your colleagues." The advantage, as it relates to teaching medical students, cannot be overestimated.

HUMAN BEHAVIOUR AND THE STUDENT

Of the many problems which face us in the further development of teaching programmes, I shall speak of two.

The first relates to substance. Our wish to help the student to acquire a basic science of human behaviour, fundamental to all of medicine, has made us realise that there is as yet no adequate unitary concept of human biology. Though the contributions of psychoanalytic psychology have been of inestimable value in providing a conceptual scheme of mind or mental apparatus, it obviously cannot serve as a general psychology, much less as a satisfactory approach to a human biology inclusive of social concepts. Throughout our teaching, and particularly in the preclinical years, we recognise that we draw our primary data from physical sciences, from biological sciences, from social sciences, from general as well as psychoanalytic psychology, and from the humanities. We are trying valiantly to accumulate the primary data which, one day, may develop and grow into a basic science of human behaviour. This ambitious, if not over-ambitious task, is being undertaken by persons like myself—fundamentally clinicians, not psychologists, biologists, or social scientists. Furthermore, we are trying to do this in a scene hardly contemplative, in the tumult and excitement of a clinical department engaged in teaching, research, and service obligations. There is much to be learnt, and we look to our colleagues in other fields as well as to ourselves for the further accumulation of knowledge and experience.

The second problem is that of method. Medical teachers and deans, often when they have had limited experience in this work, ask: "Are not students too young, too immature, too inexperienced to deal with matters relating to human emotions? Won't they become too upset?"

Our students are 21 or 22 years of age when they come to us; most of them with bachelors' degrees in arts or science; they are, in general, three or four years older than are their British and European fellow students at the time they come to the medical school. 60% of all American medical students are married before they graduate. An increasing proportion have had certain types of courses in psychology and in the social sciences in their collegiate preparation for medicine.

Many have not, as yet, earned a living; and most of our students, as persons do at this age, face the inevitable problems of relationship to authority, of planning for marriage, of acquiring the skills of their future vocation, and, more particularly, of resolving their personal identity and seeking stable value systems of belief and conduct.

For many, it is their first opportunity to deal consciously, rationally, and systematically with human experiences, such as pain, fear, shame, anxiety, and guilt, which they formerly dealt with privately. The preoccupation of many students with their own problems as these relate to vocation, marriage, and parenthood has to be recognised, and we have had to learn certain methods of teaching—in terms of timing, intensity, and content, so that we may communicate clearly. Compared with one's private physical world, one's private psychological world shows far more inertia and resistance to change. Persistent and tenacious is the belief that there is something incompatible between the exercise of intuition and the possession of conscious knowledge. We deal in many areas of human behaviour highly invested with emotional feeling—rational and irrational—such as the upbringing of children, sexual behaviour, aggression towards loved people, and differences of value beliefs between people.

It is inevitable and necessary that there should be some unrest and perplexity in the student's attempts to establish for himself a more stable, conscious, and rational body of knowledge about human behaviour. We maintain, however, that the ethos of the teaching programme should fundamentally be pedagogic and not therapeutic in design. Our experiences in the past twenty-five years indicate not only that many of our objectives can be reached, but also that the amount of serious unrest and discomfort in our students is rarely, if ever, disabling.

CONCLUSION

These are exciting times for medical education. Challenges to existing and traditional concepts and practices arise today from the societies in which we live and from the prodigious increases in knowledge. In my view, we are seeing a major reorientation—as great, perhaps, as that which took place in the 16th century in Padua with the beginning of systematic instruction in bedside teaching, or as great as the application of physics and chemistry and the quantitative method to physiology in the mid-19th century. We are seeing the beginnings of systematic approaches to man's mind, his emotions, and his relations with others. As at all beginnings, there is much fumbling and confusion, exaggerated promises, and premature structuring of concepts. But we should not be discouraged by these historically inevitable phases of growth.

For modern psychiatry to make its proper contribution, the medical school will have to provide the proper setting, with sufficient clinical and research facilities in the teaching hospital. Also it will have to encourage the recruitment and development of scholars, so that we may continue to learn from each other and gain more knowledge and skills in the understanding of human beings, sick and well, in their society and ours.

Special Articles

TAKING THE NURSING OUT OF NURSING

Transatlantic Trends

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NURSING is the concern of patients, nurses, and doctors. The interest of all three parties in the changes likely to take place in the nursing profession to meet the changing pattern of medical care and social environment is obvious from the number of articles and letters on the subject in the lay, nursing, and medical press. When discussing the likely implications of innovations, it is usually of interest to look to America where so often methods have already been tried which we are still talking about. Nursing is no exception, and I think it may be worth reporting what I saw out of the corner of my eye, and what I heard by talking with nurses, during a year spent in California doing research.

HOSPITAL CUSTOMS

I suppose the basic idea underlying the changing status of the registered nurse in the United States, as in this country, is to allow her to contribute her skill where it is most needed. The corollary is that she shall not waste it on work which can be delegated to others, and the most striking feature of the ward scene in America is the number of people ready to deal with many relatively unskilled aspects of " nursing ". Thus the food is prepared by the dietary department whose staff bring the meals to the ward and serve it to the patients. They also bring the next day's menu for the patients to order and to indicate whether they wish a large or small portion. (Without the advice of a nurse, patients often make unwise choices, and if slightly confused will order most curious diets which lead to a considerable waste of food.) Then there are ward secretaries to answer the telephone, keep the records, and deal with callers. Orderlies move patients to and from special departments, and janitors attend to the cleaning. Practical nurses, nursing aides, and licensed vocational nurses, all of whom have a short training in practical techniques, are responsible for basic nursing procedures.

Nor is time " wasted " on the doctors. The convention of escorting doctors round the wards has long since lapsed —at least in California, where these changes are perhaps more advanced than in the country as a whole. Indeed, I was there for a long time before I ever saw a doctor and a nurse speaking to each other. A large notice reminded all comers that verbal orders were on no account to be accepted. The doctors wrote orders for the nurses, who in turn wrote reports for the doctors, and each stood around reading each other's writing with never a word exchanged. Professors got as short shrift as anyone else, and could rummage around in the nursing-station looking for notes of their patients without disturbing for a moment the unhurried routine of the nurses. The quiet and sedate appearance of these cool and assured young women was in striking contrast to the bustling and harassed probationers in Britain.

What, may be asked, is left for the registered nurse to do, and how is she trained when other people seem to be doing most of what elsewhere fills the long days of the nurse in training? More and more nurses train in a college or university, and take a degree at the same time as they become registered nurses (R.N.).

In 1956 only 18% of all nurses in the United States enrolled for such courses, but in California the proportion was about 30%. They take more theoretical studies than British nurses, while practical training consists of visits to the wards for a few hours each day. These visits are planned to cover all practical aspects of nursing, and students are usually accompanied by a tutor, so that the

head nurse (sister) need not spend time showing the trainees what to do. When a nurse finishes her training, she will usually look for a career in administration, supervision, or teaching. If she wishes to join the faculty of a collegiate school of nursing, she will probably take a further university course leading to a higher degree granted after a thesis has been submitted. In 1956 more than half the faculty members of collegiate schools held a master's degree and some 3% had a PH.D.

SOME CAREERS

Some registered nurses work as private nurses, who are much more widely used than in Britain. Though a private nurse may be engaged by the patient or his relatives as a luxury, much more often, as far as I could judge, the suggestion is made by the hospital nursing staff or the doctors. For instance, if a patient needs special care, as in the first postoperative days, the family may be told that a " special " is needed. These nurses are supplied by an agency and (as might be expected) vary in competence. They are engaged by the patient, who, if he needs three to cover the 24 hours, will pay more for them than he pays for the rest of his hospital care. So as to get over this difficulty some hospitals have intensive care units, an idea borrowed from the Army. Some half-dozen ill patients of both sexes are nursed during critical periods in large rooms, where there is not only a continuous staff of registered nurses but also special equipment, such as piped oxygen and suction. Many operating-theatres have recovery-rooms of this kind which offer similar care for the first few hours after operation.

Most registered nurses make a career in administration and supervision. It is sometimes said that they have delegated so many parts of their job as nurses that when they reach these positions of responsibility they find themselves supervising activities of which they have little practical experience. But supervision is an art in itself and is taken very seriously. To understand this the wide dispersion of knowledge, or at least information, about psychology must be remembered. Many study it in High School, many more do it as a minor, if not a major, subject in college. It is part of the training for medicine, nursing, social science, and teaching. The whole population seems to be acquainted with the jargon, and parents and policemen, as well as professors and poets, speak easily of hostilities and aggressions, of learning experiences, group-interactions, and transference. Whereas we might think of the interpersonal relations of professional people as sacred ground, in the United States there are no inhibitions about analysing and examining them. I experienced the full force of this when, as an observer, I went to a conference for nurses interested in administration and supervision.

A REFRESHING COURSE

This conference was attended by some 250 nurses and was held on a delightful university campus during vacation. There were mountains in the background, a private beach on the Pacific, and an Olympic-sized swimming-pool at the back door. The lecturers were specialists in psychology, philosophy, group dynamics, industrial management, and the like. For three days these men of distinction, in their sports shirts, lived with this formidable group of women, similarly informally dressed, and a lot of ground was covered before the final barbecue on the beach.

The theme of the conference, which to us might have simply been " to find out how to get people to work better for you ", in Californian psychologese ran " to increase supervisory effectiveness in the development of human potential among members of work groups, and to improve abilities in diagnosing and treating human relations, problem situations and organisation ". One lecture on " Communication—what happens when people talk together " was illustrated by tape-recordings of conversations showing just how misunderstandings arise and can be avoided, and of how many slips there may be between what you mean, what you say, and what you are understood to have said and to have meant. Organisation theory and group dynamics dealt with experiments, mostly in industrial settings, showing how authority operated in large and small groups, the complex, yet predictable, behaviour of people in committee, and so on.

The crux of the conference lay in the small discussion groups of 10–15 nurses, each led by a psychiatrist, psychologist, or social scientist. The promise in the prospectus that the emphasis in these would be on " interaction and delegate participation " was not idle talk. At the beginning of the conference, delegates were urged to take these discussions seriously. They were invited to take risks by declaring themselves and their problems in these small groups, and to listen to feedbacks about themselves, and they were taught how to learn from this the impact they were making on other people in the group. This was of course a form of group psychotherapy: tremendous emotional situations quickly built up in these groups, and it was easy to realise that many of the participants discovered profound things about themselves which led to reorientation in their attitudes when they returned to their normal environment. I had no difficulty in believing the view of the organisers that for many of these people it was difficult after this experience ever to feel the same again when working in a group.

Members of the group to which I was attached elected to remain in ignorance of each other's status and work, and I too was incognito. This allowed a frankness of expression which might otherwise have been difficult to attain. At the end of these three tense days I wondered how many senior nurses in Britain would have submitted themselves to this experience. For it is not easy for those in authoritative positions in a hierarchical profession to expose themselves to this kind of treatment, and I was filled with admiration for the courage of these women, who, when identities were finally declared, proved to come from a wide variety of responsible posts. The most vocal and youngest turned out to be a staff-nurse, while the quiet woman, for whom this was clearly a new experience, was the matron of one of the largest hospitals in the country. There were also public-health nurses and officers in the Forces.

When the compromising nature of my profession was made known, some nurses assured me that, despite this, they did not feel any hostility towards me and did not feel threatened by my presence among them. That they should have expected to feel these reactions in the presence of a medical man indicates the curious attitude to doctors which the quest for improved status has led the American nurse to assume. It was further exemplified by a member of our group who enumerated her staff as 15 nurses, 2 social workers, 1 dietician, 1 counsellor, 1 clerk, 2 doctors, and 1 janitor.

In England Now

A Running Commentary by Peripatetic Correspondents

WHEN Helen could no longer fend for herself, and meals-on-wheels and even home-helps had done all they could, she was admitted to the former local fever hospital now given over to old ladies, mainly bedfast. When she "developed a chest" the duty houseman, who visited daily, examined her and prescribed, and on Wednesdays and the Fridays one of the visiting consultants checked her progress. The part-time assistant nurses and the sisters were kind. All of them were married women returned to nursing, and Helen saw three winters and four summers before she was gathered to the family fold. Helen was one of some seventy old ladies in this pleasant place with grassy slopes, many trees, and the finest dawn-chorus in north London.

Fred, Helen's brother, lived in the west country. After he retired from his small farm he lived in a cottage in a neighbouring village. A year ago he had a coronary and his bed was brought downstairs to ease the nursing for Lil his wife, who was once matron of a small hospital. Later Fred was found to have diabetes, and three months ago he went to the hospital in the nearby city to have partial amputation of one foot. He had been home for two months when the nursing became too much for Lil, now in her 78th year, and he was admitted to the local infirmary where about seventy beds are occupied by his invalid contemporaries. The four wards are good, and as in former years the local doctor visits daily; but an atomic reactor and an industrial chemical concern have depleted the nursing staff.

In practice Fred is still tended by Lil, who, despite her arthritis and repaired hernia, makes the return bus-journey twice daily to ensure his getting liquid nourishment, for he cannot use a cup now. Their niece recently took over for a few nights when he was pyrexial and very ill, but she has had to return to her own hospital. She is distressed when she reflects on the illusory impression of safety and care that being in a hospital can impart, and she is resolved that, on retirement, she will spend some of her days or nights as a "nurse of the future"—the part-time assistant nurse who, in hospitals for the aged and infirm at least, can give attention and show kindliness to those most dependent on the help of others.

* * *

In the idyllic early days, we travelled by canoe, hour after hour, up and down and across the shimmering Congo, to the weird chants of the *pagayeurs*. In those days you could easily read *The Lancet* from cover to cover between one dispensary and another, and there was plenty of time for contemplation against the immense backcloth of forest, cloud, and water.

Then came the Road: bulldozers, workmen, Belgian drive and finance, and we drove everywhere. A two-week journey now took only 48 hours, a complete dispensary trip a week-end. We came to grips more effectively with yaws and leprosy, and patients started to arrive on the very day their hernia strangulated.

Now we are independent, blockaded, and in economic trouble. Drug supplies are erratic, self-styled healers abound in the villages, but the work continues. We only lack one thing—that precious faintly-brown fluid that makes cars go. So once again we have taken to the water and gone is the fever and rush of modern life. *Mais il y a quelque chose qui cloche*—no *Lancet* either.

* * *

Lines written after reading a suggestion that an enemy is a "psychological necessity".

Without a foe
We wouldn't know
Into what internal conflict our unconscious
Might plunge us.*
But it's not too clear
Why our means of avoiding this neurosis must be thermo-nuclear.

* Alternative version for U.S.A. edition:
". . . unconscious
might launch us."

Letters to the Editor

EPILEPSY AND CAR-DRIVING

SIR,—May I attempt to examine the essentials of this problem? In the first place, no-one knows what proportion of road accidents results from epilepsy. Those who have studied the problem consider that epilepsy is a rare cause, but we need to know the facts. Research in this field is hemmed in with legal and administrative restrictions. Our duty as a profession is to press for research to be undertaken into all aspects of this question of medical conditions and driving safety, for woefully little is now under way.

Secondly, what is "epilepsy"? There are many forms of this condition; some dangerous in a driver, some less so. If all persons who had ever experienced an epileptic attack were to be permanently banned from driving a vehicle, a restriction would be placed on the many in order to save life and limb for a few. Some will say that it does not matter how few; that if one life is lost through an epileptic attack in a driver, all epileptics should be prevented from driving. This is an extreme view; at the other extreme is the view that so few accidents are due to epilepsy that the condition can be ignored and the calculated risk accepted. For public-service-vehicle drivers it is my opinion that the safety of the passengers is paramount and therefore that no-one should drive these vehicles who has ever had an epileptic attack. For private-car drivers a less strict view should prevail: perhaps that anyone who has not had an attack for two years and who remains under observation or treatment should be permitted to drive. But who is to ascertain the truth? Absolute prohibition of driving would lead to concealment and failure to obtain treatment, thus increasing the risk.

Fair and reasonable administration would gain the confidence of epileptics and public; to achieve this, all instances in which an applicant for a driving licence states that he suffers from epilepsy should be referred to a central (national) authority which would have power to require the applicant to remain under treatment if necessary. Compulsory notification of epilepsy is anathema to some, merely a wise precaution to others. If notification were fairly administered, epileptics might be encouraged to report their condition and so obtain authoritative advice about their safety to drive. But, Sir, we do not live in an ideal World, peopled entirely by truth-tellers, and so the problem remains with the consciences of patients and doctors; one of the few instances in which the conflict between his duty as a citizen (first?) and as a doctor (second?) may be a terrible worry for the doctor.

One final point: surely the relevant question on the driving licence application form should read "Have you ever suffered from ——" rather than "Do you suffer from ——", for the patient under treatment by an encouraging physician (as all should be) might well say to himself, "I used to" and answer "No". And what about the patient who develops a "condition" between licence renewals—now at three-yearly intervals? There should be a requirement to declare the development during this interval of the conditions listed on the licence application form, and perhaps of others—if research shows these conditions to be associated with an accident liability greater than we as a community wish to accept.

London Transport Executive,
London, N.W.1. L. G. NORMAN.

YET ANOTHER COLLEGE

SIR,—In a recent broadcast, Sir Eric Ashby discussed the Challenge of Expansion of the Universities.[1] He pointed out that their prime purpose was to transmit truth (in contradistinction to pursuing it, in his context). This, surely, should be the main aim of our colleges, whether their foundations are old, new, or prospective.

Psychology is a subject on which it is very difficult to

1. *Listener*, June 1, 1961, p. 959.

think clearly, and in which heresies thrive. The chastening effect of comment and criticism is most important, therefore, for psychiatrists. Indeed, many, realising this, have enriched their own intellectual experience and that of their general-practitioner colleagues, by arranging psychiatric seminars for the latter to attend. To discourage the formation of their own college, as you do in your leading article of June 24, is, therefore, to discourage a deep-felt need. We rightly rejoice when colonial territories attain self-government and become independent nations. Their new status brings them life, vigour, and sense of responsibility. The case for the foundation of new colleges by branches of the medical profession is in close parallel. The logical corollary to the argument in your leading article would be to suggest the fusion of the three Royal Colleges to form a mighty monolith, a prospect which does not bear thinking about.

In branches of medicine where the standard of practice is variable, the status of the best suffers unjustly for the shortcomings of the worst. It is understandable, therefore, when the best wish to raise the general standard—perhaps even by establishing a higher qualification.

Doubtless, psychiatrists have much to contribute to the practice of their general medical and surgical colleagues in a general hospital. They differ, however, particularly as the Mental Health Act becomes implemented, in that their main effort is to be exerted in the community outside. Their presupposition that psychiatry differs much from the rest of medicine in contrast to, say, cardiology or dermatology is, therefore, perfectly reasonable.

Barton-on-Humber, Lincs. S. H. F. HOWARD.

NEEDS AND BEDS

SIR,—National statistics provide an average from which there will be some deviation in various parts of the country; the data for Birmingham in the recent paper by Cross and Yates [1] are an interesting example. Comparison of the Birmingham statistics with figures obtained by applying national rates to their population shows:

(*a*) The Birmingham population was younger than the average. The psychiatric bed estimates were made for people aged 15 and over, and of these Birmingham had 745 males and 772 females per 1000, compared with 756 and 783 for the country as a whole.

(*b*) The Birmingham admission-rates were below the national average at ages under 65, and higher than average at 65 and over. In particular, the rate for elderly women was 436 per 100,000 compared with 304 for England and Wales.

(*c*) The average annual admissions during 1953–55 were 1026, compared with 1042 expected, but of these totals, admissions at ages 65 and over were 236 compared with 177 expected.

(*d*) The proportion of Birmingham patients leaving by discharge or death in successive periods after admission was higher than average at ages 15–34, somewhat less than average at ages 35–64, and still lower at ages 65 and over.

In consequence, if the Birmingham results are applied to the standard million population of England and Wales, 1954, the number of patients becoming long-stay cases would be males 63, females 148, total 211; compared with the actual number of males 66, females 103, total 169. Here again there was an excess of females aged 65 and over, of 90 compared with the national figure of 43.

It appears that in 1953–55 the Birmingham hospitals were carrying a smaller load of resident patients and had less admissions than the average for the country as a whole. They had, however, an excess number of female residents aged 65 and over, a relatively high admission-rate for this group and a comparatively low rate of leaving hospital, resulting in an excessive number of potentially chronic patients.

Such differences from the national average may well be connected with the types of alternative accommodation available. Before regional data can be used as a basis for national estimates, the variations from the average need to be demonstrated and explained.

General Register Office, London, W.C.2. EILEEN M. BROOKE.

1. Cross, K. W., Yates, J. *Lancet*, 1961, i, 989.

CONTROL OF CROSS-INFECTION

SIR,—The article by Dr. Gillespie and his colleagues (June 17) was of great interest to us. Cross-infection in the surgical and gynæcological wards of this group has been a problem for some time. This is particularly true of the gynæcological department, which has not only inadequate buildings but also a three-year waiting-list to contend with. Extra beds have thus become a permanent feature of the wards.

It seems worth emphasising one particular measure we have found helpful—the use of the ampholytic germicidal agent TEGO.

Walter and Kunsdin [1] described the relationship between the bacterial count on the floor and airborne bacteria. Thus it was thought that if an efficient method of cleaning could be found the general background of bacterial milieu might be favourably affected.

Frisby [2] was impressed with TEGO. After helpful conversations with him we introduced this compound into the Women's Hospital. It was used for daily theatre cleaning using a spray, and weekly ward cleaning using a squeegee mop. A trial is also being made of terylene ward-cubicle curtains which can be dipped in the TEGO solution and allowed to dry.

After the use of this substance the numbers of cases of staphylococcal wound infection showed a gratifying fall. The details will be published later.

The Royal Hospital, Wolverhampton. H. EVERLEY JONES
C. H. L. HOWELLS.

1. Walter, C. W., Kundsin, R. B. *Surg. Gynec. Obstet.* 1960, **111**, 412.
2. Frisby, B. R. *Lancet*, 1959, ii, 57.

MEDICAL EMIGRATION

SIR,—Dr. Alexander (June 3) has put his finger on a point of vital importance to the continuation of the preeminence of British medicine in Africa.

As he says, it is sad but true that the fire and crusading spirit of British medicine appears to have died. No longer do Britain's young doctors and nurses look to their still underdeveloped Commonwealth relatives to provide challenging and rewarding surroundings to practise professions which even today maintain for some an aura of dedication.

If the present lack of enterprise on the part of British medical practitioners and nurses is not reversed, it will not be long before the medical and nursing professions of other countries, with more ambition, initiative, and drive, will stream in to fill the vacuum now existing, particularly in Africa.

The Federation of Rhodesia and Nyasaland is in an especially favourable position in that it is a land with one of the finest climates in the world, steeped in the British tradition, and determined to become a leader in Africa in the field of medicine. The proposed medical school of the University College of Rhodesia and Nyasaland, to be sited at Salisbury, which will operate in the closest collaboration with the University of Birmingham whose medical degrees will be awarded, will set the seal on this preeminence.

Dr. Alexander said that many of these former colonial

outlets are closed; but the Federation is, I am glad to say, still wide open to any doctor, nurse, and for that matter members of many related professions and groups who still have a feeling in the bottom of their hearts that they are not fulfilling their life's mission, in what Dr. Alexander rightly calls an over-doctored country.

D. M. BLAIR
Secretary for Health,
Federal Ministry of Health.

Salisbury,
Rhodesia and Nyasaland.

"BREACH OF CONTRACT"

SIR,—Mr. H. V. Capstick (June 17) raises an issue of the utmost importance affecting all N.H.S. practitioners. As he points out, the effect of the powers entrusted to disciplinary bodies of the N.H.S. has been to abrogate the rights possessed by doctors as citizens under the Common Law. Every one of the six points raised by Mr. Capstick is entirely relevant and, in my experience, to consultants equally with general practitioners.

As chairman of the ethics and professional affairs committee of the Association of Clinical Pathologists I have personal experience of two cases in which the professional careers of consultants in the N.H.S. were ruined as the result of action taken within the administrative framework of the N.H.S., without reference to the Common Law.

Whether or not the final action taken in these cases by the administration was justified is beside the point; the fact is that in both of them those concerned were denied the rights belonging to every citizen under the Common Law.

This state of affairs demands much more vigorous action on the part of the whole medical profession of this country than it has yet aroused.

S. C. DYKE.

Wolverhampton.

INTENSIVE-CARE UNITS IN AMERICAN HOSPITALS

SIR,—Mr. Carner's letter (July 1) is misleading if it intends to convey the impression that recovery rooms are being replaced by intensive-care units in the United States. Although these units are rapidly becoming a feature of all American hospitals the main purpose is not to replace recovery rooms, but to economise in nursing staff and at the same time save money for the patient. They also remove the need for keeping patients in the recovery rooms for long periods, a purpose which they were never intended to fulfil.

Most American hospitals are designed to cater for paying patients who demand the privacy of a single or at most a double-bedded room, and a ward (or division as it is called) comprises up to 30 or 40 such units. This arrangement makes adequate supervision of critically ill patients difficult for the regular nursing staff (which is provided on a much less generous scale than in this country). Consequently special nurses have to be employed on a 24-hour basis at a cost of about £15 per day and the patient has to foot the bill.

It has therefore been found not only economical in nursing staff but cheaper for the patient to be cared for in intensive-care units. Although the overall charge per bed is more than for a single room it includes the cost of special nursing and other services, such as oxygen and suction, for which there would otherwise be a special charge.

But these units, apart from being equipped with piped oxygen and suction together with various monitoring devices, do not differ materially from our own acute medical and surgical wards, and in fact are a return to the old system of open-ward nursing.

Even so they present certain problems. Some patients resent the loss of privacy and relatives the restrictions on visiting (usually five minutes every hour). These can usually be overcome by the intern, whose duty it is to explain the advantages of constant supervision and the immediate availability of apparatus for resuscitation and the recording of vital signs. Moreover, in the new hospitals "family rooms" are available for relatives adjacent to the intensive-care unit.

Nurses in these units after a time become frustrated because as soon as a critically ill patient is over the worst he returns to the division; the nurse loses touch, thus missing the sense of vocational fulfilment which arises from nursing a moribund patient back to early convalescence.

D. A. BUXTON HOPKIN.

Charing Cross Hospital,
London, W.C.2.

THE *Pseudomonas pyocyanea* PROBLEM

SIR,—Nine years ago Yow [1] drew attention to a relative increase in the incidence of infections due to pseudomonas. This year Barber [2] considers that, of the gram-negative bacilli, it is the most serious menace, and is beginning to rival the infamous pyogenic staphylococcus as the hospital scourge. In a preliminary communication Lubsen et al.[3] mention that *Pseudomonas pyocyanea* was often present in urinary tract infections, despite the use of an antiseptic, while Lowbury et al.[4] obtained heavy growths of *Ps. pyocyanea* from 38 out of 101 burns. In view of these reports a brief account of an investigation carried out last year to determine the bactericidal effect of thiomersalate ('Merthiolate') on four hospital strains of *Ps. pyocyanea* may be of interest.

A formidable bacterial challenge was prepared by diluting an overnight broth culture (18 hours at 37°C) 1 in 200 with additional nutrient broth (pH 7·5), mixing and distributing in twelve 50 ml. flasks. Thiomersalate was then added to nine of these, so that three flasks contained a final concentration of 1 in 10,000 thiomersalate, with three containing 1 in 100,000, and three with 1 in 1,000,000. The remaining three flasks, designed to act as controls, received saline. One flask of each dilution and a control flask were then kept at 37°C, 22°C, and 4°C, subcultures being made at intervals from 30 minutes to 32 days, after adding the thiomersalate. The subcultures were made in thioglycolate broth with subsequent incubation at 37°C for 10 days. From the accompanying table it can be seen there were no survivors isolated after $2^1/_2$ hours exposure to 1 in 10,000 thiomersalate, and none at 24 hours (1 day) when the concentration was 1 in 100,000 and the temperature maintained at 37°C. There was an increase in survival time at lower temperatures and concentrations. When the temperature during exposure was maintained at 22°C survivors were isolated at $2^1/_2$ hours from 1 in 10,000, and at 2 days, when the concentration was 1 in 100,000. At the lowest temperature

Interval between adding thiomersalate and subculture			Temperature of incubation and concentration of thiomersalate (C = control flasks)											
			37°C				22°C				4°C			
Days	Hr.	Min.	10^{-4}	10^{-5}	10^{-6}	C	10^{-4}	10^{-5}	10^{-6}	C	10^{-4}	10^{-5}	10^{-6}	C
		30	+	+	+	+	+	+	+	+	+	+	+	+
	2	30	−	+	+	+	+	+	+	+	+	+	+	+
1	..	..	−	−	+	+	−	+	+	+	+	+	+	+
2	..	..	−	−	+	+	−	+	+	+	+	+	+	+
4	..	..	−	−	+	+	−	−	+	+	−	+	+	+
8	..	..	−	−	+	+	−	−	+	+	−	+	+	+
12	..	..	−	−	+	+	−	−	+	+	−	−	+	+
32	..	..	−	−	+	+	−	−	+	+	−	−	+	+

+ = Survivors isolated from any strain after subculture.
− = No survivors.

1. Yow, E. M. *J. Amer. med. Ass.* 1952, **149**, 1184.
2. Barber, Mary. *J. clin. Path.* 1961, **14**, 2.
3. Lubsen, N., Boissevain, W., Faas, H., *Lancet*, 1961, i, 921.
4. Lowbury, E. J. L. Lilly, H. A., Miller, R. W. S. Cason, J. S., Jackson, D. M. *ibid.* p. 1318.

(4°C) survivors were subcultured from 1 in 10,000 at 2 days and from 1 in 100,000 at 8 days.

Dr. Knights' exhortation (Feb. 18) to use an antiseptic capable of lethal activity in high dilution, when used against epidemic strains of staphylococci, might be applied to the pseudomonas.

Miss J. M. Beavon and Mr. P. Maybury kindly supplied the strains used in this study.

Eli Lilly & Co., Ltd.,
Basingstoke. RONALD D. MACKENZIE.

FŒTAL HÆMORRHAGE INTO THE MATERNAL CIRCULATION

SIR,—We should like to reinforce the opinion of Dr. Apley and his colleagues (June 24) that the Kleihauer technique [1 2] offers a simple method of diagnosing massive transplacental hæmorrhage (T.P.H.) into the maternal circulation.

Skill and experience is needed to detect very small quantities of fœtal blood in the maternal circulation; but the recognition of massive T.P.H. presents no serious difficulties. It is to be hoped that the method will soon become standard practice in obstetric units.

We have performed this technique extensively for the past two years. Attention to a few practical points greatly improves the test. The best results are obtained with fresh buffer solution. Kleihauer et al. originally suggested that the buffer should be used for ninety seconds, but we have obtained better results with a period of five minutes. The reaction depends on the buffer coming into intimate contact with the alcohol-fixed blood-film, since otherwise uneven elution will occur. We flood the slide with buffer solution (at 37°C) and agitate it gently on a slide rack throughout the five-minute elution period. The slide is then washed in running water for about thirty seconds and dried with filterpaper. The blood-film can then be examined; any fœtal cells present will stand out clearly as dark refractile bodies. Staining of the dried film is unnecessary. Difficulty is occasionally encountered with slides dirtied by dust particles from the atmosphere. This can be avoided by using fresh films; if complete examination cannot be carried out immediately it is better to keep the blood specimen (using oxalate or sequestrin) than to make alcohol-fixed films and examine them later.

The results can be seen in figs. 1 and 2. On fig. 1 is a typical massive T.P.H. (high power); the film was taken from a mother whose infant was found to have a hæmoglobin level of 6·3 g. per 100 ml. after delivery (this case has already been reported elsewhere [3]). Fig. 2 shows the low-power appearance of massive T.P.H., and is taken from a case in which the infant was noted to have a hæmoglobin of 9·8 g. per 100 ml. Both babies recovered spontaneously with oral hæmatinics. In neither instance was any obvious predisposing cause detected.

1. Kleihauer, E., Hildegard, B., Betke, K. *Klin. Wschr.* 1957, **35**, 637.
2. Zipursky, A., Hull, A., White, F. D., Israels, L. G. *Lancet*, 1959, i, 451.
3. Finn, R., Clarke, C. A., McConnell, R. B., Sheppard, P. M. *Nature, Lond.* 1961, **190**, 922.

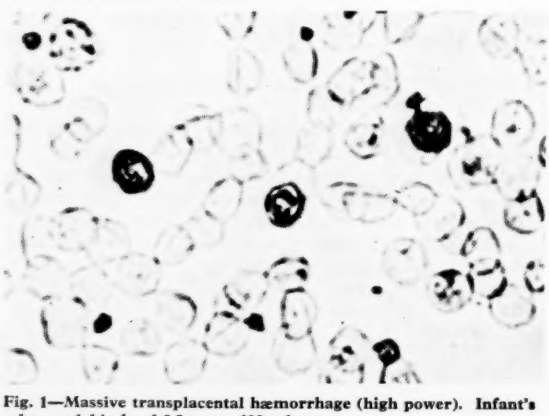


Fig. 1—Massive transplacental hæmorrhage (high power). Infant's hæmoglobin level 6·3 g. per 100 ml.

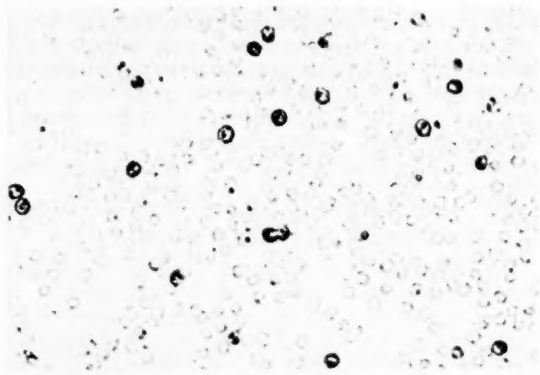


Fig. 2—Another case (low power). Infant's hæmoglobin level 9·8 g. per 100 ml.

The one serious drawback to this technique occurs in ABO heterospecific pregnancies where any ABO incompatible fœtal cells entering the maternal circulation are destroyed almost instantaneously. We have recently published evidence [4] that T.P.H. cannot be detected by acid elution in such circumstances. It follows, therefore, that the Kleihauer technique cannot be used for detecting massive T.P.H. in ABO heterospecific pregnancies. As about 80% of pregnancies are ABO homospecific, the Kleihauer technique is of obvious value, but a negative result in suspicious clinical circumstances should always be followed up by a check on the ABO status of mother and infant. The diagnosis of massive T.P.H. in ABO heterospecific pregnancies can be very difficult to prove; the possible methods have been reviewed by Goodall et al.[5]

Massive T.P.H. may be defined as transplacental hæmorrhage of sufficient magnitude (probably in excess of 50 ml.) to lead to recognisable signs of blood-loss in the fœtus. Wickster [6] was the first to draw attention to the two clinical pictures found in massive T.P.H. This condition is to be sharply differentiated from smaller bleeds which occur in up to 20% of pregnancies and are of no immediate clinical significance to the baby.

If the hæmorrhage has occurred during or shortly before delivery, the clinical picture in the infant will be that of cardiovascular collapse due to loss of circulating blood. Thus there is pallor, loss of muscle-tone, and tachycardia, with failure to revive with oxygen, but a dramatic response to transfusion. Diagnostic confusion may arise in lengthy cerebral anoxia and cerebral trauma which also result in pallor and loss of muscle tone (asphyxia pallida). In these cases, however, the pulse-rate is usually slow, there is delay in establishing regular respirations, cerebral signs may be present, and oxygen administration improves the colour. If, on the other hand, the hæmorrhage has been slow or has occurred some time before delivery, the fœtal circulatory system will have compensated for the loss in blood-volume, and the child will present simply with pallor.

The first presentation—namely, that of cardiovascular collapse following delivery—is of great importance, as its rapid recognition will save life. Massive T.P.H. is not a rare condition and it is to be hoped, therefore, that the widespread use of the Kleihauer technique will lead to a more general awareness of this treatable condition.

We should like to thank Mr. C. H. Walsh and Dr. Anne E. McCandless for permission to record these cases.

Sefton General Hospital, Liverpool,
and Department of Medicine,
University of Liverpool. C. M. DURKIN
RONALD FINN.

4. Finn, R., Clarke, C. A., Donohoe, W. T. A., McConnell, R. B., Sheppard, P. M., Lehane, D., Kulke, W. *Brit. med. J.* 1961, i, 1486.
5. Goodall, H. B., Graham, F. S., Miller, M. C., Cameron, C. *J. clin. Path.* 1958, **11**, 251.
6. Wickster, G. Z. *Amer. J. Obstet. Gynec.* 1952, **63**, 524.

THE HANDICAPPED

SIR,—I should like to comment on your interesting leading article of June 10. The survival of the severely and multiply handicapped infant raises ethical doubts, when one appreciates first-hand what a lifelong worry the parents have to face: I say that advisedly, while still realising the remarkable way in which these families meet and face the situation. It imposes many difficult restrictions, burdens, and strains on domestic life, sometimes tragically detrimental.

Much of the stimulus to greater interest in the educational world has come from the top, at the Ministry of Education: in discussion with members of the Special Services Branch, I have been very impressed with the knowledge and humanitarian interest shown.

Broadly, I strongly agree with two points in your thesis: the need for continuity of management and for coordination of services. All too often, still, both leave much to be desired: for instance, the child you mention, with hydrocephalus and a paraplegia from a myelomeningocoele, may get excellent orthopædic treatment to mobilise him, but the urological needs may be hopelessly neglected and he is left with irreversible renal damage, and the social stigma of incontinence. The medical and educational programmes should equally be integrated.

The team required and the method of approach demand careful thought and planning: the sheer complexity of the problem makes a systematic basis and an experienced team imperative: both take time to create, and for that reason, I strongly support the idea of special assessment centres.

Planning and parent advice (counselling sounds too pompous) should start soon after birth. One big risk, is the multiplicity of agencies which may get involved: infant-welfare centre, family doctor, pædiatrician, orthopædic surgeon, and school medical officer. I do not believe the general practitioner has the time, nor does he see enough disabled children, to build up the all-round experience, and many such children need full hospital investigation. Equally, the school doctor may not be in the closest touch with clinical work, unless he is associated with a university or a teaching department of child health. For example, with the limb-bud anomalies, there may be associated cardiac or pulmonary defects, or a blood dyscrasia, calling for hospital and laboratory services. Usually, too, it involves two-stage planning: first, the immediate programme, and then the long-term implications: the latter entails forecasting based on experience of possibilities and probabilities.

To play the part of coordinator in this type of team work calls for special training and familiarity with the work of psychologist, teacher, physiotherapist, speech therapist, occupational therapist, almoner, apart from a range of medical consultant services, orthopædic, urological, neurosurgical, psychiatric, pædiatric; and also a knowledge of most of the social legislation, welfare services, further training, youth employment, and disablement resettlement officer aspects. Further, it is, I think, essential to be methodical and have a basic common denominator by which to test results, but not necessarily another subspecialty.

The yardstick used here for the past $5^1/_2$ years has been a careful functional assessment of the degree and type of daily life handicap: this has proved a real advance, and has helped to clarify objectives and limitations.

For example, an employment hazard may be the unsteadiness of choreoathetosis, or inability to protect resulting from poliomyelitis of both arms. Functionally, an individual may be *more* handicapped in mobility after a spinal fusion for a paralytic kyphoscoliosis, though the latter may be essential for other reasons, but the additional handicap must be assessed and interpreted. The sequence of operations may require critical evaluation: for instance, it may be desirable to complete hip surgery needing a plaster hip spica before doing an ileal loop; otherwise, the hip surgery may be almost impossible.

These examples emphasise the need for a method applicable to a wide range of conditions, and providing sufficient flexibility to allow effective reviewing—that is, the clear demonstration of gains or losses. This we have found in the study of daily life: it has answered a number of our former difficulties in assessment; and it provides a common language and terminology in a team.

Working to this pattern involves a measure of breach of medical confidence, but I find this unavoidable when pulling together the threads of a complex medicosocial problem, and the benefits outweigh the losses.

You state "an essential member of team would be an *educational* psychologist": I would qualify that by saying a *clinical* psychologist, because in the very young child, it is important to know more of the medical implications: the effect on developmental progress of sensory loss or lack of mobility due to motor paralysis of the legs. The psychologist's report should certainly be available to both medical and educational sections of the team, and also to therapists; and mutual discussion should be encouraged.

We have just built a new 20-bedded unit for exactly these purposes of comprehensive assessment and planning: this has been made possible by a very generous donation from the Coxen Trust. This unit is designed specially for this phase of our work, and is opening in the autumn, after several years' careful thought have been given to the function and design.

Chailey Heritage,
(Craft School and Hospital),
Chailey, Sussex.

E. P. QUIBELL
Medical Administrator.

PREMATURE AFFIRMATION OF DEATH?

SIR,—Concerning your article on this subject (May 6, p. 1007) may I draw attention to the paper by Kevorkian,[1] who has succeeded in determining the time of death by observing the fundus oculi. His method, besides being simple and requiring only an ophthalmoscope, has other applications; it can be used in differentiating between apparent and true (biological) death.

Phoenix, Arizona. HUBERT J. ADLER.

STEAM PENETRATION INTO CONTAINERS FOR SURGICAL DRESSINGS

SIR,—Dr. Fallon's very useful paper last week goes astray at one point. So-called nylon bags are permeable to steam—as stated—but are designed for the older type of autoclave (downward-displacement) where the pressure changes are as great (or even greater) than in the modern high-vacuum steam steriliser; but the changes of pressure take place *relatively slowly* in the downward-displacement autoclave. Nylon bags—heat-sealed—are undamaged by the changes of pressure in the downward-displacement autoclave, because these changes of pressure take place *slowly*.

But in the modern high-vacuum autoclave the changes of pressure occur very rapidly, the pores in the nylon bags cannot allow such rapid movement of steam, and the bags burst.

There is, of course, air in the nylon bags when the dressings are put in and the bags sealed. This air is allowed to escape through the minute pores (through which steam also passes) when the vacuum is applied before the steam is admitted to the sterilising chamber. I am very doubtful whether the bags are burst by air, as this would occur before the steam was admitted; and there is no evidence that the nylon bag bursts at this stage.

The remedy was suggested to me by a traveller for the firm who make these nylon bags. The method was further developed by one of our senior technicians, Mr. Philip Church. He sealed a short length of aluminium tubing into a corner of the bag; this tubing is slightly crimped at both ends and filled fairly firmly with sterile white cotton-wool. The cotton-wool filter allows air and steam to escape freely and prevents the admission of organisms at any stage. For good sterilisation it is

1. Kevorkian, J. *J. forensic Sci.* 1961, **6**, 261.

essential that air should be removed from the nylon bags before exposure to steam. Mr. Church's little gadget allows this and prevents the nylon bag bursting.

St. Margaret's Hospital,
Epping, Essex. FRANK MARSH.

LIMITATIONS OF MEDICAL CARE ATTRIBUTABLE TO MEDICAL EDUCATION

SIR,—The one false assumption which mars Professor McKeown's thesis (July 1) propounding a combined health service based on the hospital is his remark at the foot of the first column that the existing curative services are based primarily on hospitals.

The hospital service in this country is a large chromium-plated auxiliary service available to the general practitioner for the minority of his cases with which he cannot cope either alone or by bringing a consultant to the patient's own home.

The majority of ordinary people do not have any medical care in hospital except for trauma, acute surgery, or possibly a single illness of some sort during their active lives. A 5% minority pass through the mental health service. The aged and decrepit enter hospital often for medicosocial reasons.

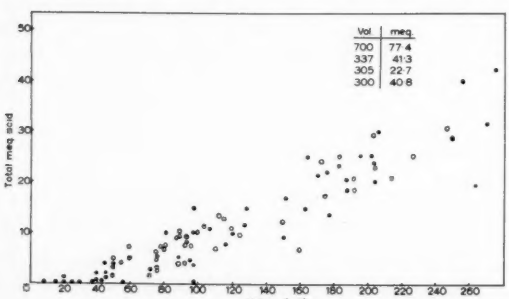
At all other times the family doctor provides continuous and adequate care throughout a lifetime. He is the linchpin of the whole service. If there is to be any change of emphasis in our services it will have to be on the lines of a more comprehensively trained general practitioner prepared to take over preventive work.

Health Department,
Brighton. W. S. PARKER
Medical Officer of Health.

SECRETORY BACKGROUND TO GASTRIC ULCER

SIR,—It has been suggested that "the most direct measure of gastric secretion is the volume of juice produced on maximal stimulation" [1] and that "pathological variations in gastric secretory behaviour, designated as hypersecretory or hyposecretory, should be evaluated in terms of the rate of secretion (i.e., the volume of secretion per time interval or per fractional specimen), rather than in terms of the acidity of the fraction".[2]

It has, however, been my impression that the volume of juice collected is no guide to the amount of acid secreted by the



Each dot represents one complete augmented histamine test. Details at top right are for four black circles outside the figure.

stomach, and it is therefore with much interest that I read Dr. Ball's article (June 24) on the acid secretion in 50 patients with gastric ulcers. I have taken the data plotted in fig. 1 of his article and converted the milliequivalents per litre (mEq. per litre.) to total milliequivalents (total mEq.) which, I believe, is the most satisfactory index for expressing the test findings since it combines the volume, mEq. per litre, and duration of collection of the juice. These (open circles in the accompanying figure) I compare (black circles) with my own observations on 50 patients whose acid-secreting ability was determined during the investigations of their iron-deficiency or megaloblastic anæmias; only 2 had gastric ulcers. It will be seen that the two sets of results fit remarkably well, and that there is a wide scatter throughout. This is particularly marked when the volumes are small—e.g., around 100 ml. the scatter is from 0·02 mEq. to 16·0 mEq.

It is therefore necessary to calculate the total mEq. of acid in each individual patient when the ability of the stomach to secrete acid is being assessed.

Nuffield Department of Clinical Medicine,
The Radcliffe Infirmary,
Oxford. O. A. A. BOCK.

1. Callender, S. T., Retief, F. P., Witts, L. J. *Gut*, 1960, **1**, 326.
2. Hollander, F., Penner, A. *Amer. J. dig. Dis.* 1939, **5**, 739.

COMPENSATION FOR CUPIDITY?

SIR,—My suggested remedies for accident neurosis may be "cumbersome". Dr. Reynard's (July 1) is clearly irrelevant. Most cases seen here affect workers in coal-mining or other heavy industries, who are fully covered by industrial health services.

Newcastle upon Tyne. HENRY MILLER.

PSYCHIATRIC SEQUELÆ OF CHRONIC EXPOSURE TO ORGANOPHOSPHORUS INSECTICIDES

SIR,—In its struggle to eradicate malaria, the World Health Organisation may soon find it necessary to use organophosphorus (O.P.) insecticides to control mosquitoes that have become resistant to dicophane (D.D.T.), benzene hexachloride (B.H.C.), or dieldrin, the insecticides that have been successfully used to date. It is, therefore, important that any statement about untoward effects believed to be attributable to an exposure to organophosphorus insecticides should be scrutinised carefully so that the appropriate action may be taken.

Dr. Gershon and Professor Shaw (June 24) claim to have established a connection between exposure to O.P. insecticides and the development of psychiatric disturbances.

They state that "16 cases of chronic exposure" have been investigated. No single figure of the blood-cholinesterase activity of their patients is produced as evidence that they had absorbed any of the O.P. insecticides at the time they were working with them. Nor do they provide any of those facts about the incidents in which exposure was said to have occurred which it is customary to give in accounts of occupational poisoning. Some psychiatric details of 4 cases are provided while the other 12 cases are briefly listed. The "disturbances" in some (cases 5, 6, 14, and 15) seem to be hardly serious enough to be described as "psychiatric". One patient, after being in hospital with an acute schizophrenic episode for 2 weeks, is said to have benefited from injections of atropine and the oxime, pyridine 2-aldoxime methiodide. Yet it is well known that cholinesterase that has been inhibited for 48 hours or more cannot be reversed by oximes.

A paragraph headed Effects on the Central Nervous System lists practically every disturbance to which the mind is heir, but in the absence of any comment from the authors, the list lacks significance in relation to the cases described. It might, however, be compared with the facts given by Holmes and Gaon [1] in their analysis of 449 cases of poisoning by O.P. compounds in each of which the level of blood-cholinesterase inhibition arising from exposure was known. Under Central Nervous System, Holmes and Gaon list the following symptoms:

Headache — *Increased perspiration*
Dreams, poor sleep — Dizziness
Fatigability — Tremor and twitch, fasiculation
Nervous and irritable. Mood changes — Paræsthesia and cold

Only those symptoms in italics occurred in more than half the 49 patients most severely affected, in whom there was a 40% or greater inhibition of blood-cholinesterase. Only 19 of these

1. Holmes, J. H., Gaon, M. D. *Trans. Amer. clin. climatol. Ass.* 1956, **68**, 86.

same patients showed the symptoms " Nervous and irritable. Mood changes ". Yet Gershon and Shaw claim to have diagnosed psychiatric disorders in 8 out of 10 greenhouse workers. Of the 600 cases of exposure to O.P. compounds encountered by Holmes and Gaon in 5 years, 37 had had 3 or more exposures. Some were said to show personality changes and 25 of them were separately interviewed by 2 investigators. " Each group listed 6 men with persistent personality or work performance changes yet only one name was common to both lists." The personality changes recorded were mainly irritability and forgetfulness, and Holmes and Gaon make no mention of schizophrenia or depression which the Australian authors found so frequently.

There have been many hundreds of cases of poisoning by O.P. insecticides in Japan,[2] but Dr. Namba, who has been responsible for treating and saving the lives of many of these unfortunate people, could recall no case of consequent mental illness when I questioned him on this point in New York earlier this year.

Gershon and Shaw open the final paragraph of their discussion with the sentences: " It may be objected that our results are due purely to chance and that exposure and mental change are not related. It is true that our results have not been analysed statistically and they were drawn from the community at large." As many cases of poisoning by O.P. compounds have occurred the world over and as the claims of Gershon and Shaw are not consistent with at least one very thorough investigation, surely it is incumbent upon both authors and journals to take more care at least in choosing the title of their papers if it is felt necessary to publish observations of doubtful significance. It hardly seems likely that an incidence of 80% for a complication of a type of poisoning which has been so frequent and widespread would have escaped the attention of everyone hitherto.

In the prevailing climate of opinion nothing too bad can be said about the harmful properties of pesticides. Nevertheless it would be unfortunate if premature and possibly ill-founded claims of their ability to produce psychiatric disorders should restrict the use of O.P. insecticides in lifesaving programmes of disease eradication.

Toxicology Research Unit,
Medical Research Council Laboratories,
Carshalton, Surrey. J. M. BARNES.

SIR,—The conclusions reached by Dr. Gershon and Professor Shaw conflict with experience of the clinical course of poisoning by organophosphorus compounds.

Hundreds of cases of acute poisoning by insecticides in this group have been recorded in countries other than Australia and many more people will have worked with these compounds in the ways described by the authors. In the State of California alone there were reported for the year 1957 229 cases of poisoning due to organic phosphate insecticides. Of these systemic poisoning occurred in 189 cases, due in 151 to parathion or compounds of greater toxicity, in 12 to malathion or compounds of lesser toxicity, and in 26 to unspecified organophosphorus compounds.[3]

In none of the cases previously reported have psychiatric symptoms of more than transient nature been recorded. Recovery from poisoning is complete, and rapid, provided that treatment with atropine in adequate doses, and the more recently developed oximes, is given promptly. It is known that a few compounds in this group are capable of causing demyelination. New organic phosphorus compounds are tested for this effect and discarded as potential insecticides if it is demonstrated.

The organophosphorus insecticides, along with chlorinated hydrocarbons and other types of pesticides, have been of immeasurable value in the fields of agriculture, horticulture, and public health. At a time when uninformed public opinion is reacting emotionally to the possible long-term harmful effects of *any* pesticide—a possibility for which there is no supporting evidence—I trust that conclusions about the psychiatric sequelæ of " chronic exposure " to organophosphorus compounds will be drawn from controlled observations rather than from impressions.

London, S.W.1. P. LESLEY BIDSTRUP.

PROFESSIONAL SECRECY AND THE LAW

SIR,—Dr. Keating says that if a sufficient number of doctors felt strongly enough about their moral duty to keep professional confidences secret, the law could be changed. Surely that is obvious. After all, our patients think that we are honourable men when they trust us with their inmost secrets. Surely it is our duty to face prison, even death, rather than divulge these secrets to anybody.

Galway. B. J. O'DRISCOLL.

FACTOR STIMULATING CELL DIVISION IN CULTURED LEUCOCYTES

SIR,—We are prompted by Dr. de la Chapelle's letter of June 17 to report our own inexpensive preparations from *Phaseolus vulgaris* beans, Canadian red or Cannellini (price 1*s.* 6*d.* per lb.), of substances which stimulate mitosis in leucocyte cultures, and which agglutinate red cells.

The method used, based on that described by Rigas and Osgood,[1] for the extraction of mucoprotein hæmagglutinin from *P. vulgaris* beans, was as follows:

The beans (100 g.) were soaked in physiological saline (0·85%, 80 ml.) for 26 hours at +5°C, macerated, and allowed to stand with more physiological saline (320 ml.) for 23 hours at +5°. The gross insoluble matter was removed by filtration through a Buchner funnel, and the pH of the filtrate (about 300 ml.) was adjusted to 6 (long-range indicator paper) by 2*N* hydrochloric acid (1–2 ml.). Absolute ethanol (40 ml. per 100 ml. of filtrate) at −19°C was added, and the precipitate (I) which formed was separated by centrifugation for about 20 min. at 1800 r.p.m. at +5°C. The supernatant was decanted and ethanol containing 10% ethyl ether (170 ml. per 100 ml. of supernatant) at −19°C was added. The precipitate (II) was removed by centrifugation as before. The precipitates were dried at room temperature over silica gel in a vacuum desiccator (2–3 days), to yield brittle solids which were powdered. The yield of I was 0·9 g. and of II 0·2 g. The products from the Cannellini were yellow and those from the Canadian red beans were pink. They have been stored at +5°C.

Doubling dilutions of a 1% suspension in physiological saline, with physiological saline (1/2–1/512) were used to test the serological activity of the preparations against group A_1, A_2, B, and O red cells, by reading the agglutination macroscopically, after 5 minutes. The cells of all groups were agglutinated equally, to a dilution of 1/16 by red and Cannellini I, 1/128 Cannellini II, 1/256 red II, 1/256 Difco P, 1/2 Difco M, 1/32 Difco original product, and to 1/128 by the red bean extract before ethanol addition.

In the preparation of leucocyte cultures (from 20 ml. of heparinised blood) leucocyte-rich plasma was separated from red cells by the addition of 1% suspensions of the precipitates I (0·04 ml.) or II (0·02 ml.), followed by centrifugation at 400 r.p.m. for 5 min. Then the addition of 0·03 ml. more of the same suspensions to the white cells suspended in Glaxo TC 199 medium and homologous plasma (final volume 6–8 ml. and final cell concentration 1000–2000 cells per c.mm.) produced a high rate of mitosis observable after 2–3 days at

2. Namba, T., Hiraki, K. *J. Amer. med. Ass.* 1958, **166**, 1834.
3. Kleinmann, G. D., West, I., Augustine, M. S. *Arch. environ. Hlth*, 1960, **1**, 118.

1. Rigas, D. A., Osgood, E. E. *J. biol. Chem.* 1955, **212**, 607.

37°C. Hence, all four precipitates possess sufficient mitogenic activity for the satisfactory preparation of leucocyte cultures for chromosome analysis.

We are now investigating the relationship between the mitogenic and agglutinating activity of substances prepared from beans of other species of the genus *Phaseolus*.

We suggest that until more is known about their structure, factors extracted from plants which exhibit mitogenic activity, be referred to as phytomitogens.

Galton Laboratory, University College, London, W.C.1. RUTH MARSHALL.

Department of Chemistry, Birkbeck College, London, W.C.1. B. CAPON.

TEENAGE MORALS

SIR,—Just because I agree so heartily with much of Dr. Comfort's review in your issue of June 17, I feel bound to take issue with him on two of his important conclusions.

To take the last first: in his final paragraph Dr. Comfort reminds us that the safest way for children to advance through the dangers of adolescence is by having mature parents. Yes, indeed: in different words this has been echoed down the centuries, millennia before we psychiatrists arrived to point and underline the objective reasons for making it. But of what *use* is it to keep rubbing it in to worried parents? The process of parent-condemnation seems to me just as destructive as that process of teenage-condemnation which Dr. Comfort so rightly decries. I write this with concern, not as a parent, but as a child psychiatrist. Too many otherwise balanced parents have come to feel guilt-ridden, anxious, and insecure, and therefore resentful, in the management of their offspring, unable to trust their own reasonable judgment. This difficulty alone is quite enough to undermine the affection and respect which, for happy and stable family life, parents rightly ought to command in their own children. And for this difficulty we psychiatrists have largely only ourselves to thank. Perhaps we may forgive ourselves when we consider that the evolution of psychology would be impossible without various stages of imbalance on the precarious way. But let us not continue to reinforce this most damaging of errors.

Secondly, on the crucial matter of moral standards: it seems a strange contradiction in terms to write, as Dr. Comfort does, of a contemporary change in standards. (At least, this is surely what he means by his vaguer term of a change in "public morals".) For if we allow that morality in the sexual sphere is a relative and changeable matter, what have we got to say about morality in other spheres—for example, in relation to physical aggression and stealing, to Negro-baiting, and to racial pride? Being psychiatrists, we try to understand why our patients fall short, sometimes disastrously, of what so often turns out to be even their own best inner standard; and through understanding we try to help. But this is surely irrelevant to the fact that objective moral standards do exist, and have existed in Western civilisation from its beginning, and before that from the time of Moses. We are each one of us individually free to accept or to reject the part or the whole of this morality; but if we choose to reject, let us do so in all honesty, without hypocritically claiming a "new" morality.

Even without the benefit of good example in the home, intellectual clarity as such is often the greatest help to confused adolescents, whatever their intelligence. To supply this seems the minimum responsibility which any adult can exert, who happens to come into contact with youngsters in turmoil. There appears to me to be no real difficulty in explaining the essentially simple principles involved. Further, it is often most reassuring to unformed minds to discover that even no reasonable adult would claim perfection in these matters, but at best a sincere aspiration. In other words, they thus learn that human conflicts are at bottom the same in us all, however divergent their form between the generations.

The main reason, however, why this unemotional approach can be so helpful to disturbed youth is that it provides a solid step towards mental liberation of the moral conflict as such from its usual entanglement in tormenting parent-child relationships, with all their subjective distortions of value and judgment. To those who would contest this statement with the reminder that adolescence is in its nature an age when strong instinctive egoistic impulses may be overriding, I would reply that it is also an age when spontaneous idealism and pride of intellect may also play a powerful part. Anxious preoccupation about the instinctual life has led us to undervalue, if not to overlook, those very qualities in the young which cry out for our understanding and cooperation. I submit that it is *these* which we reject at our peril.

London, W.8. JUDITH WATERLOW.

DAMAGE TO CHROMOSOMES BY THERAPEUTIC DOSES OF RADIOIODINE

SIR,—In their preliminary communication (May 6), Miss Boyd, Dr. Buchanan, and Dr. Lennox report on chromosomal aberrations due to ^{131}I in therapeutic doses.

The statement "These findings raise the question whether radioiodine therapy can cause leukæmia" suggests that these may be permanent changes. But the longest follow-up period (case 6) is only seven days; and, whereas the white-blood-cell survival is four to seven days, that these anomalies persist is unproven.

Against this, one might cite the abnormality in case 6 before the course of therapy. This has been attributed to previous therapy with ^{131}I. Though this may be likely, we do not know whether this anomaly was present before the original therapy; and, even if it was due to previous treatment, we do not know whether or not there was a larger proportion of abnormal cells previously which were gradually "dying out". This point of view is suggested by the data from case 6, since the percentage of "normal cells" (i.e., those with the modal number) increased progressively in each successive post-radiation study.

Harbor General Hospital, Torrance, California, U.S.A. SEYMOUR N. HERSCHBERG.

GENETIC FACTORS ON THE X CHROMOSOME

SIR,—The excellent paper by Miss Jacobs and her coworkers [1] was particularly interesting in respect of the cases with abnormal X chromosomes. Although their conclusions are entirely consistent with the available data alternative possibilities seem worthy of closer consideration.

If it is accepted, as is most probable, that the abnormal chromosomes with median centromeres are X-derived isochromosomes, then three simple inferences about the position of genetic factors on the X chromosome may be made:

(1) A factor for sex-chromatin manifestation is present in the long arm of the X chromosome.

(2) A factor for normal stature development is present in the short arm of the X chromosome.

(3) A factor for normal gonadal cortical development is present in the short arm of the X chromosome.

These inferences are consistent with the clinical nuclear sexing and chromosomal data in the cases (5 and 15) reported if these abnormalities are caused by simultaneous deletion from both arms of the X chromosome. Of several possible mechanisms the most probable is crossing-over in a pericentric inversion. The practical importance of this hypothesis is that some such inversions might be detectable by the occurrence of

1. *Lancet*, 1961, i, 1183.

abnormal centromere position in one of the X chromosomes of the mother of the patient.

Alternatively, more complex inferences must be made. The interpretation of long or short arm deletion implies the presence of at least two factors for sex-chromatin manifestation, one in the long and one in the short arm of the X chromosome, and the presence of at least two factors for gonadal cortical development, again one in each arm.

It is now known that a colour-blind patient with chromatin-positive Turner's syndrome [2] has an X-derived isochromosome with duplication of the long arm of an X chromosome, together with a paternally inherited X chromosome which carries a gene for colour-blindness. Together with Dr. Lindsten's report of a mosaic,[3] this suggests that the colour-blindness loci are also situated in the short arm of the X chromosome. This would appear to be the first instance in man in which it is possible to localise a known gene to a segment of a chromosome.

Department of Surgery,
Queen's College,
Dundee.

JOHN S. S. STEWART.

APPROVED NAMES

SIR,—Dr. Asher (June 3), in his attack on the British Pharmacopœia Commission approved names, seems to have missed the point. Approved names are not " prolix creations of unimaginative officials ", but names devised or selected in accordance with ten guiding principles to which I would refer Dr. Asher.

Most advances in medicine during the past quarter century have followed advances in one or other branch of organic chemistry. In fact, organic chemistry, either as biochemistry or as pharmaceutical chemistry, is the mainstay of medicine today. It follows that if full use is to be made of the tools placed at the physician's hand, some understanding of organic chemistry is essential. Though, very often, a physician's ignorance of organic chemistry is virtually, if not quite, complete, he might at least make the effort to use the name of a drug which has its basis in the source or chemical structure of the substance.

The conflict between the British Pharmacopœia Commission and the drug houses in the formulation of drug names has aptly been likened to a contest between a commando and a boxer. The commando is likely to win because he obeys no rules, while the boxer is bound by a code. This point alone is sufficient to discredit the pidgin-english nicknames imposed on valuable modern drugs by the drug houses with the apparent object of maintaining the state of confusion concerning the nature of the drugs they advertise.

This suppression of the approved name of a compound forces the prescriber to rely more and more on proprietary names and thus fall right into the hands of commercial interests. The resulting confusion was illustrated by two doctors who were talking about the treatment of epilepsy: Dr. A. said he preferred ' Eptoin ', while Dr. B. said he was convinced that ' Epanutin ' was more effective. Both are brands of sodium phenytoin. This confusion, which can be really dangerous and not a little discrediting to the doctors, could be easily avoided by the use of approved names only. The mental and physical effort required is not great and the results can be very satisfying.

The British Pharmacopœia Commission face a difficult task which, generally speaking, they accomplish very well. When they do fail to adhere as closely to the guiding principles as we might like they deserve constructive and sympathetic criticism, not derision.

The decision to use approved rather than proprietary names should rest not on a desire to " please the Minister " but (on an altogether higher plane) on professional grounds.

Selly Oak Hospital,
Birmingham.

A. P. LAUNCHBURY
Deputy Chief Pharmacist.

2. Stewart, J. S. S. *Proc. R. Soc. Med.* 1959, **52**, 817.
3. *Lancet*, 1961, i, 1228.

SIR,—I was very interested in Dr. Asher's letter, but I am disturbed by its main implication—that it saves the Ministry money if the official rather than the proprietary name is written. In the list of 22 drugs in your issue of May 13, every one is, in fact, issued only as a proprietary preparation, covered by patent rights, and none is otherwise available in an " official " form. No additional expense is involved by the Ministry if these preparations are prescribed by trade name, nor is anything saved if they are prescribed by their official name; there is only one proprietary form in which any of them can be dispensed.

Romford,
Essex.

A. R. RITCHIE
Managing Director,
Macarthys (Wholesale Chemists) Ltd.

OCULAR COMPLICATIONS FROM CHLOROQUINE

SIR,—You mention (June 17) that corneal deposits are a fairly frequent event during both chloroquine and hydroxychloroquine treatment. It is, however, worth pointing out that there are apparent differences in the incidence of this complication in chloroquine and hydroxychloroquine treatment.

Thus, Hjorth and Vesterdal [1] report a series of patients who have been on long-term treatment with either chloroquine or hydroxychloroquine. Of 90 patients on chloroquine, 27 had changes in the corneal epithelium. Of 66 patients on hydroxychloroquine, however, such changes were observed in only 2.

Moreover, Kersley and Palin [2] observed only 1 case of corneal complications when hydroxychloroquine was given as a single medication.

From the data, it seems that, as far as corneal deposits are concerned, hydroxychloroquine is very much safer.

Bayer Products,
Surbiton, Surrey.

K. BOHEIMER
Director.

AUTOMATION IN CLINICAL BIOCHEMISTRY

SIR,—We agree with Dr. Tárnoky (April 22, p. 880) on the usefulness of the automatic analyser for clinical biochemical analysis and share the general enthusiasm shown for this revolution in technique in the country. Our two and a half years' experience with this machine, however, prompts us to comment on two points which he raises.

We feel very strongly that the analyser should not be tended by an unskilled person. In our opinion, only a fully trained and experienced technician can be expected to appreciate the nature and significance of the processes and the results produced, and hence show the sense of responsibility needed in clinical and scientific work and in running this machine. Only such a trained person can decide, for example, which estimations require repetition, and perform dilutions. The unskilled machine-minder might well not detect and correct the major and minor failures to which this machine, as any other, is liable. Such minor faults as pin-hole perforation of the dialysing membrane, manifold tubing failure, and excessive wear of platten springs, may then result in a long run being completed without their appreciation. This can only tend to increase the number of stray results which Dr. Tárnoky is rightly so anxious to eliminate, or lead to many wasted man-hours in the repetition of estimations, with delay and disruption of a tightly planned programme for the machine.

The suggestion that the automatic analyser might be situated close to the diabetic clinic for blood-glucose estimations strikes us as being usually unnecessary. The availability of simple, accurate and rapid glucose-oxidase methods, which can be easily performed in an outpatient clinical room if necessary,

1. Hjorth, N., Vesterdal, E. *Ugeskr. Læg.* 1959, **123**, 278,
2. Kersley, G. D., Palin, A. G. *Lancet*, 1959, ii, 886.

with the minimum of apparatus, makes this estimation of low priority for automation. The automatic analyser is thus more efficiently employed with other tests unless an exceptionally large number of blood-glucose estimations have to be performed in a very short time.

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R. J. HURST
J. E. MIDDLETON.

INFLUENCE OF DIETARY ELECTROLYTES ON MÉNIÈRE'S DISEASE

SIR,—We have been studying the effect of varying the dietary sodium and potassium in patients with Ménière's disease.[1] This work arose from our view [2] that electrolytes were actively transported across a membrane between the general circulation and the labyrinthine fluids—a view that is supported experimentally.[3 4]

Clinical experience suggested that patients with Ménière's disease had fewer acute attacks when their salt intake was low; and hence either a low-sodium diet or a high-potassium diet or supplement have been prescribed. But it has long been known that a *high*-salt intake does not necessarily mean more frequent or more severe attacks, and some workers have used sodium loading as a method of investigation,[1 5 6] principally to avoid the unpleasantness to the patient of a low-salt diet. The various methods of sodium loading were certain to produce a retention of sodium when deoxycortone was used as a salt-retaining hormone, but even during this true sodium loading attacks of vertigo or acute deterioration of cochlear function did not increase.

TABLE I—ESTIMATE OF PERSONAL DIETARY TURNOVER OF SODIUM (Mrs. K.)

Serial day of investigation	Regime	Body-weight st. lb.	Body-weight kg.	Urinary sodium output in mEq.	Known sodium supplement mEq.	Sodium in diet
5	Ward diet+34 mEq. sodium as NaCl	12–8½	80·25	161	− 34	= 127
6	Ward diet+34 mEq. sodium	12–7½	79·75	106	− 34	= 72
7	Ward diet+68 mEq. sodium as NaCl	12–9¼	80·75	139	− 68	= 71
8		12–8¼	80·1	199	− 68	= 131
9	Ward diet+102 mEq. sodium as NaCl	12–9	80·5	261	− 102	= 159
10		12–10	81·0	159	− 102	= 57
11	Ward diet+102 mEq. sodium as NaCl	12–10	81·0	164	− 102	= 62

Average turnover value for days 5–8 = 100 mEq.
Average turnover values for days 5–11 = 97 mEq.

As deoxycortone is a long-acting hormone and can overcome the normal physiological mechanisms of sodium homœostasis, in our subsequent investigations we replaced it by the more physiological and shorter-acting aldosterone; we loaded the patient with sodium chloride, using aldosterone to enhance sodium retention; and short treatments with sudden changes of load were studied to determine their relationship, if any, to the attacks of vertigo or to significant variation in auditory threshold.

No attack was precipitated by injections of aldosterone (1 mg. intramuscularly daily for three or more days), whether accompanied by a sodium load or not. But several patients had attacks while under observation in hospital. They had been on a scheduled sodium intake for some time previously; their urinary output of sodium had been measured and plasma-electrolyte levels of many of them were known. They were also regularly weighed. Assuming that, when the weight was steady, a period of sodium equilibrium had been reached, we used the data of the cumulative balance of this period to calculate a "personal turnover-rate" for sodium. Several of the patients had attacks during a sodium diuresis. At least 1 patient was in negative cumulative sodium balance at the time of the attack, despite the added salt, which would ordinarily have been assumed to have produced positive sodium loading.

TABLE II—CUMULATIVE BALANCE FOR SODIUM (Mrs. K.)

Serial day of investigation	Na intake (dietary Na = 100 mEq.)	Na output mEq.	Daily balance	Cumulative balance	Cumulative balance, dietary Na = 90	Cumulative balance, dietary Na = 110
1	100	195	−95	−95	−105	−85
2	100	38	+62	−33	−53	−13
3	100	21	+79	+46	+16	+76
4	100	123	−23	+23	−17	+63
5	134	161	−27	−4	−54	+46
6	134	106	+28	+24	−36	+84
7	168	139	+28	+52	−18	+122
8	168	199	−31	+21	−59	+101
*9	202	261	−59	−38	−128	+52
10	202	159	+43	+5	−95	+105
11	202	164	+38	+43	−67	+153
12	202	306	−104	−61	−181	+59
13	202	246	−44	−105	−235	+25
14 Low-salt diet	50	256	−206	−311	−441	−181
*15 Low-salt diet	50	192	−142	−453	−583	−323

* Ménière's attack, objectively observed.

Another patient had a characteristic attack when from the cumulative balance curve a diuretic phase might have been expected, had not an increased salt load been given 12 hours previously (according to a pre-arranged schedule and without knowing the state of balance at that time). This further increased salt loading resulted in a positive sodium balance despite an increased rate of urinary sodium excretion.

The principles of the calculations are as follows (see tables I and II):

A fore-period on ordinary ward diet is important; the patient is told not to eat much salty food on any one day, and as steady an intake as possible is attempted. Plasma-sodium values and the daily weight (in the same clothes and at the same time each day), together check that sodium homœostasis has been achieved. This is the ideal situation, seldom completely fulfilled, and in practice one has to be satisfied with a few days' preparation; the patient is then given a known additional amount of sodium chloride in tablet form, and the previous diet is continued. The supplementary intake is then increased every 2 or 3 days: plasma-sodium, and urinary sodium output are measured, and body-weight noted daily. A period of 3, or, if possible, more days is chosen when body-weight is steady; and the known additional sodium intake is deducted from the urinary output to obtain a "personal turnover-rate" for dietary sodium. This is an average figure which will seldom be precise for any one day; but the cumulative balance sheet must be accurate since all the patients end the treatment with approximately the same body-weight as they started and without any evidence of the dehydration of serious sodium deficiency. A relatively simple calculation on the basis of the cumulative balance sheet gives fairly narrow limits within which the personal turnover-rate must fall.

As, in the first instance, we are concerned with the slope of the curve at the time of an attack and not with the absolute level, this method provides a definite answer to whether sodium gain or loss precedes or is concurrent with an acute Ménière episode. Occasionally it is also possible to show that there was an actual negative sodium balance (negative to that individual's equilibrium point) at the time of the attack.

1. Harrison, M. S., Naftalin, L. *Proc. R. Soc. Med.* 1958, **51**, 624.
2. Naftalin, L., Harrison, M. S. *J. Laryng.* 1958, **72**, 118.
3. Weille, F. L., Irwin, J. W., Jako, G., Holschuh, L. L., Weille, A. S., Stanley, C. A., Rappaport, M. B. *Ann. Otol., &c., St. Louis*, 1958, **67**, 858.
4. Jako, G., Weille, F. L., Palmer, P. E., Irwin, J. W. *ibid.* 1959, **68**, 733.
5. Perlman, H. B., Goldinger, J. M., Cales, J. O. *Laryngoscope, St. Louis*, 1953, **63**, 640.
6. Golding-Wood, P. H. *J. Laryng.* 1960, **74**, 480.

The data suggest that patients with Ménière's disease may have either an exaggeration of the normal swing of sodium balance by which homœostasis is effected or a disturbance of hormone balance that makes the water-balancing and the salt-regulating mechanisms " out of step ". Neither need be far outside the normal range, but the deviation may be enough to prevent a " sensitised " cochlea or vestibular apparatus from coping with the sudden changes of concentration.

With these ideas in mind we are now giving our patients with Ménière's disease a double supplement of sodium and potassium chloride, with or without added citrate. (The salts are best given, from the point of view of absorption, as a mixture, but many patients do not like this form and prefer tablets: coated tablets should not be used.) Our purpose is to " iron out " electrolyte fluctuations and so to stabilise as much as possible the salt and water hormone systems. In this way significant sodium diuresis should be unlikely (as it would be on a low-salt regimen) and the ion-exchange mechanisms in the membranous labyrinth have to face only slight fluctuations in sodium and potassium concentrations. A steadier state in the endolymph can thus be maintained. A regimen of salt supplements is not only pleasanter for the patient and easier to follow, but also cheaper.

These investigations are continuing and we hope shortly to report our findings in full.

The general method we have outlined may have applications in other investigations in which the normal relationship between the electrolyte and water balancing systems is thought to be disturbed.

Our thanks are due to the patients who kindly cooperated in the inquiries, and to Dr. A. K. Pittman, director of clinical research, Ciba Laboratories Ltd., for supplies of aldosterone and of hydrochlorothiazide (' Esidrex '), which was occasionally used to enhance a diuretic phase at the end of the salt-loading period.

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L. NAFTALIN
M. SPENCER HARRISON.

THE GENERAL PRACTITIONER AND THE HOSPITAL

SIR,—Dr. James (June 24) is right to emphasise that practices are too big. Even in an average-sized practice of about 2000 patients for each doctor, many will bewail the fact that there is not enough time to deal with everything as well as could be desired. It is not as simple as he suggests, however, and the ability to cope with problems must vary in different individuals with varying speeds of work, and with differing interests and beliefs. Inevitably some with reforming zeal will make the criticism, as Dr. James has done, that the load of work falls too heavily on the hospitals as a result of the pressure of work on the family doctor.

Ancillary aids in the form of services by laboratories and X-ray departments are available to the family doctor now in many areas, as they are here. The doctor may thus go very far, if he wishes, along the line of investigation of a particular case. Apart from blood-counts and chest X-rays, in some areas if the doctor wishes to have an E.E.G. or a urinary 17-ketosteroid estimation, he is at liberty to ask for them. But is it right to insist that increased facilities be given? The excessive use of diagnostic aids may often hide the true diagnosis.

In asking hospital consultants what are the most time-consuming cases in their outpatient clinics, the answer often is " the neurotic patient ". In my view this is a greater criticism of the family doctor than the fact that he has missed a case of Kimmelstiel-Wilson syndrome, or an unusual heart disorder. By interesting himself in the neuroses, the general practitioner who feels able, or keen to do it, will save many patients from repeated visits to the surgery with disguised emotional disorder. He may save more patients from visits to hospital, sometimes only to be returned at once with the note that " physical disease has been excluded ". Sometimes he may save the patient from the even more expensive (in terms of time, further mental ill health, and money spent by the nation) dizzy round from one consultant to another. This is a side of medicine which more and more general practitioners are trying to practise. Although it is time-consuming, it is interesting and often rewarding. It should be an antidote for Dr. James's disgruntled practitioner who thinks he is " just a glorified clerk ".

Nottingham. BRENDAN JACOBS.

SIR,—The ideas put forward by Dr. James in his article of June 24 follow in many essentials the lines of thought originally advanced in the Collings report on General Practice in England Today.[1] That the deterioration in standards of practice began before the inception of the National Health Service, and was then intensified by it, and that the best standards of practice were preserved in the country, can still be accepted as valid. But the experiences of the past decade require that other propositions should be modified. The " leaders of all branches of the profession " certainly bear some responsibility, but is the Government entirely blameless for inadequate progress in general practice? In their evidence to the Pilkington Commission on remuneration the representatives of the Ministry of Health defended the capitation-fee method of remuneration [2] and the continuation of much of the machinery of the old National Health Insurance scheme, including a central pool, which was admitted to be to the advantage (financially) of the Government.[3]

An important remedy, advocated by both Dr. Collings and Dr. James, is the encouragement of the formation of partnerships and group practices. This is the only positive policy that has been followed under the N.H.S., in the organisation of general practice, by both the profession and the Ministry, yet it is quite clear that this does not provide the answer to what general practice should be like today. In fact, at least as good a case has been made out for the " personal doctor " practising individually,[4] while at the opposite extreme the idea of the health centre has been revived as a result of such reports as those by Dr. Sluglett on the existing health centres in this country,[5] and Dr. Silver on the comprehensive service provided by the organised Montefiore Medical Group and Hospital in New York.[6]

I think Dr. James is incorrect in suggesting that the general practitioner does not need to return to hospital work. As he says, " clinical medicine must be seen as an indivisible whole "; and this suggests, too, that the specialist should, conversely, treat patients under domiciliary as well as hospital conditions, as was originally envisaged in connection with health centres. Perhaps such integration of work would be facilitated if regional hospital boards, with appropriate broadening of their representation, became responsible for the general planning of the health services of the regions, which was one of the suggestions made by Dr. Galloway in his article on the Integration of the Preventive and Curative Health Services.[7]

All interested in good medicine in general practice will agree wholeheartedly with Dr. James on the harm caused by the " principle of small profits and a large turnover ", and therefore in the necessity to discourage the

1. Collings, J. *Lancet*, 1950, i, 555.
2. *Brit. med. J.* 1958, i, suppl. p. 220.
3. *ibid.* p. 214.
4. Fox, T. F. *Lancet*, 1960, i, 743.
5. Sluglett, J. Report on Health Centres. Medical Practitioners' Union, London. 1960.
6. Silver, G. A. *Proc. R. soc. Med.* 1961, **54**, 449.
7. Galloway, J. F. *Lancet*, 1960, ii, 34.

maintenance of unduly large numbers of patients per practitioner.

London, N.W.2. J. J. SEGALL.

RUPTURE OF THE POSTERIOR URETHRA

SIR,—Mr. Wilkinson's article (May 27) and the subsequent correspondence are of considerable interest since road accidents are making these injuries more common.

Divisions of the urethra at the apex of the prostate, in my experience, are most often associated with severe displacements of the bony pelvis and somewhat comparable displacements of the two ends of the urethra. The displacements of the bony pelvis often allow an adequate exposure of the perineal injuries, but after passing the two-way catheters the displacements (in two planes) of the divided urethral ends are often seen to be quite considerable, then suture cannot be effected without considerable tension, if at all, unless both ends are mobilised with, perhaps, further damage to the urethra.

The answer to this and, indeed, many other problems in the repair of such complicated injuries is surely the highly organised units mentioned in Mr. Qvist's letter (June 24). The displacements of the bony pelvis and the traction division and displacements of the perineal tissues are one wound. The soft-tissue components of this wound cannot always be satisfactorily approximated until the bone displacements are reduced and held, as Dommisse [1] has shown they can be. Then, and only then, can "the fundamental principles of wound treatment" be followed—namely, the *early* and close approximation of all the components of the wound.

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CARCINOID SYNDROME

SIR,—It is generally accepted that flushing in the carcinoid syndrome should be ascribed to the fact that the tumour periodically releases serotonin, which in its free state is transported by the blood to the periphery and produces capillary dilatation in the skin.

There is no evidence, however, that free serotonin is present in the arterial blood; and strong evidence against the above theory is that the endocardium of the left side of the heart is not damaged (as is the right side) in the carcinoid syndrome, and that flushing attacks cannot be reproduced by intravenous injection of serotonin. The latest conception is that the flushing attacks are not produced by free circulating serotonin, but that serotonin is released locally by adrenaline.[2]

Our view about the flushing is that 5-hydroxytryptophane develops in carcinoid tumours and is transported by the blood to the peripheral tissues, where it is deposited, probably after being transformed into serotonin. Adrenaline releases the serotonin deposits, which produce flushing attacks, and the attacks subside when the free serotonin is carried away by the blood. This conception is supported by the following clinical observations.

In 1960, we saw a 36-year-old woman who had had flushing for 4 years. Carcinoidosis was diagnosed at laparotomy. The urine contained an increased amount of 5-hydroxyindole acetic acid. Flushing attacks appeared from 10 to 15 times daily, provoked by stooping or by meals. The attacks were accompanied by vomiting, but never by diarrhœa.

Immediately before a spontaneous attack of flushing, the left brachial artery was compressed by the cuff of a blood-pressure manometer. Though the skin was typically coloured in other areas, no flush was seen distal to the armlet. When the general flushing had disappeared, the armlet was removed, and distal to the site of compression typical flushing now appeared.

This experiment proves that spontaneous flushing attacks are humorally mediated, and that the humoral influence persists after flushing has disappeared. The flushes must, therefore, depend on peripheral factors too. The humoral factor demonstrated might be adrenaline; if so, flushing attacks might be prevented by adrenolysis.

By infusion of 50 mg. phentolamine over a period of 5 hours, it was, contrary to expectation, only possible to reproduce very few, mild attacks of flushing, and the patient was able to eat without vomiting. During the flushes, the skin over the vein infused maintained its normal colour and appeared as a pale stripe.

Hence phentolamine prevents both general and localised flushing, and there is every probability that adrenaline is the natural flush-provoking factor. The peripheral factors may to some extent be defined by another experiment.

The brachial artery was compressed during maximum flushing of the arm. When flushing disappeared from the other arm, the colour did not fade distal to the armlet; here the skin gradually became reddish and cyanotic, and did not pale till the armlet was removed.

The experiment shows that the peripheral factor is active as long as blood-circulation is interrupted, but disappears when the circulation is normal. Consequently, this factor must be humoral and arise peripherally through the mediation of adrenaline. According to the prevalent conception this factor must be serotonin.

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1. Dommisse, G. F. *J. Bone Jt Surg.* 1960, **42B**, 432.
2. Peart, W. S., Andrews, T. M., Robertson, J. I. S. *Lancet*, 1961, i, 577.

SIMPLE METHOD OF DEMONSTRATING LACTIC ACID DEHYDROGENASE ISOENZYMES

SIR,—In an annotation [1] you pointed out the possibilities of enzyme electrophoresis to detect lactic acid dehydrogenase isoenzymes. Unfortunately the complexity of the method described limits its usefulness in clinical laboratories.

Clinical applications of enzyme electrophoresis, by a technique which is much more suitable for routine work, were described by Wieme and his coworkers.[2–6] The same technique was used by van Sande et al.[7] to study lactic and malic acid dehydrogenase in cerebrospinal fluid. Another simplified procedure for demonstrating lactic acid dehydrogenase was recently described by Blanchaer [8] in the light of its clinical applications.

We have developed a method in our laboratory which we think is even more convenient. We found that a current histochemical technique—reduction of tetrazolium salts combined with agar-gel electrophoresis—demonstrates lactic acid dehydrogenase activity. Tetrazolium salts have also been used to demonstrate lactic acid dehydrogenase activity in starch gel.[9–10] Our method has the advantage of a short electrophoretic run (25 min.), and enables an impression of the quantitative proportions of the different isoenzymes to be obtained by densitometry followed by planimetry.

Electrophoresis is carried out with 8 μ of serum, on Wieme microscope slides.[11] Next the slide is incubated for an hour in the following medium:

Sodium lactate (*M*)	1·0 ml.
Diphosphopyridine nucleotide (10 mg. per ml.)	1·0 ml.
Sodium cyanide (0·1 *M*)	1·0 ml.
Magnesium chloride (0·005 *M*)	1·0 ml.
Phosphate buffer (0·5 *M*, pH 7·4)	2·5 ml.
Nitroblue-tetrazolium (1 mg. per ml.)	2·5 ml.
Phenazine methosulphate (1 mg. per ml.)	0·25 ml.

After incubation, when four or five purple zones appear, the slide is rinsed with water and, if desired, densitometry can be carried out on the wet slide, using an interference filter with maximum transmission

1. *Lancet*, 1960, ii, 1131.
2. Vuylsteek, K., Wieme, R. J. *Belg. Tijdschr. Geneesk.* 1958, **14**, 750.
3. Wieme, R. J. *in* Protides of the Biological Fluids; p. 236. Amsterdam, 1959. (Proceedings of the 6th Colloquium, Bruges, 1958.)
4. Wieme, R. J., Demeulenaere, L. *Acta gastro-ent. belg.* 1959, **22**, 69.
5. Wieme, R. J. Studies on Agar Gel Electrophoresis; p. 482. Brussels, 1959.
6. Wieme, R. J. *Clin. chim. Acta*, 1959, **4**, 461.
7. Sande, M. van, Karcher, D., Lowenthal, A. *in* Protides of the Biological Fluids; p. 108. Amsterdam, 1961. (Proceedings of the 8th Colloquium, Bruges, 1960.)
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9. Markert, C. L., Moller, F. *Proc. nat. Acad. Sci., Wash.* 959, **45**, 753.
10. Dewey, M. M., Conklin, J. L. *Proc. Soc. exp. Biol., N.Y.* 1960, **105**, 492.
11. Wieme, R. J. *Clin. chim. Acta*, 1959, **4**, 317.

at 590 mμ. Another possibility is to fix the plate for half an hour in the following fixative: ethanol 70 vol., acetic acid 5 vol., distilled water up to 100 vol. The plate is subsequently dried covered with filter-paper (to absorb buffer salts). Then densitometry can be carried out on the dry plate. If protected from daylight these slides can be kept indefinitely. In the light a background slowly develops. It is also possible to stain the dry plate with amidoblack to determine the positions of the protein fractions.

The results obtained so far with this simple technique agree well with those of other techniques.

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FIBROCYSTIC DISEASE AND SWEAT

SIR,—The final paragraph of your leading article of May 13 stated that " The high salt content of bronchial mucus in fibrocystic disease certainly predisposes to staphylococcal lung infections. . . ." This statement may cause confusion in its present form and should not go unchallenged. Rather than having a high salt content, the bronchial mucus in fibrocystic disease has an unusually low sodium and potassium content, as compared with bronchiectatic sputum. It is thought by some that this low sodium content and a relatively high calcium content may have bearing on the molecular size of the mucoid material and may be contributing to the marked viscosity of cystic-fibrosis mucus. In fact, it has been proposed that the therapeutic use of hypertonic salt solutions merits evaluation. I refer to the study by Chernick and Barbero.[1]

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SPECIFIC ANTIBODY AGAINST GASTROINTESTINAL MUCOSA

SIR,—The letter by Dr. Gray and others (July 1), describing negative results in their search for serum-antibodies to colon in patients with ulcerative colitis, could have an unfortunate effect in discouraging further investigation of a possible autoimmune factor in this disease. We cannot explain their failure to repeat the positive results of various workers (e.g., Asherson and Broberger [2]), but an important consideration must be the uncertainty about the serological activity of the colonic antigen. We should also like to draw attention to the possible value, in a study of this sort, of employing techniques capable of detecting non-precipitating in addition to precipitating immunological reactions.

Earlier this year at symposia held by the Tissue Culture Association and by the Association of Clinical Pathologists,[3] we gave an account of the preparation of specific heterologous anti-sera against gastrointestinal mucosa. Rabbits were immunised with a microsomal fraction of normal human-colon mucosa and the resulting antiserum was absorbed with human kidney micro-some material to remove species-specific activity. The reaction between the absorbed serum and the colon antigen was non-precipitating and gave a complement fixing titre of 1:500. It was also demonstrated by intense fluorescent antibody staining of gastrointestinal mucosa [4]; the distribution of staining and its correlation with conventional histochemical reactions suggests that acid mucopolysaccharide is a component of the antigen. No fluorescent staining of any other human tissue was obtained though some reaction occurred with the intestines of certain animals. Especially interesting, in relation to the loss of organ-specific antigens which occurs in malignancy,[5 6] was the absence of staining of gastrointestinal cancers; benign polyps stained uniformly while lesions, thought by conventional criteria to be " premalignant ", showed distinct patchy staining.

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M. G. MCENTEGART
J. E. FOTHERGILL
I. B. PORTEOUS.

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SIR,—Dr. Gray and his colleagues record their failure to find any evidence of the presence, in the serum of patients with ulcerative colitis, of antibodies reacting with extracts of human colonic mucosa. I have similarly examined sera from 41 patients with ulcerative colitis, also with completely negative results.

Saline extracts were prepared from colons removed surgically from patients with ulcerative colitis and from patients with carcinoma of the rectum or colon. Immediately after they had been excised the mucosa was scraped off and stored at −20°C until the extracts were prepared.

All sera were tested both by the agar diffusion technique and by complement-fixation tests. The agar diffusion tests were performed in narrow-bore tubes using serum doubling dilutions of 1/2 to 1/6 against antigen fourfold dilutions of 1/1 to 1/64. The complement-fixation tests were performed by the micromethod described by Belyavin,[1] using serum doubling dilutions of 1/1 to 1/28 and antigen doubling dilutions of 1/1 to 1/16.

Sera from 33 of the patients were tested against extracts from both ulcerative colitis and carcinoma cases, and the remaining 8 against an extract from an ulcerative colitis colon only.

None of the patients had been treated with steroids.

No precipitin lines were found in the agar diffusion tests. The occasional absence of lysis in some of the dilutions in the complement-fixation test was not considered to be due to the presence of antibody.

This work was carried out before Broberger and Perlmann [2] published their findings. Their method of antigen preparation differed from mine in that they made phenol-water extracts, and in order to reduce bacterial contamination they used colons from newborn infants who died soon after birth before they had been fed. While it is possible that the discrepancy between their results and mine might be due to their having used the phenol-water method of extraction, it does not seem likely that the bacterial flora could, in my investigation, have made any significant alteration to a colonic mucosal antigenic factor since the colonic mucosa was placed at −20°C within 15–20 minutes of the surgical excision of the specimens.

This work was made possible by a grant from the Governors' Discretionary Fund of Westminster Hospital. I am grateful to the staff of the Gordon Hospital for sera and material from their patients.

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of Westminster Hospital,
London, S.W.1. W. M. EDGAR.

SPECIFIC TRANQUILLISER TOXICITY

SIR,—The following instance of severe sensitivity to a specific phenothiazine derivative seems of interest in view of the small dose and lengthy effects.

Boardman et al.[3] refer to extrapyramidal effects from as little as 6 mg. trifluoperazine daily; and Benaim (personal communication) has seen severe tremor and torsion spasm of the neck in 3 patients, 1 of whom had only received altogether 4 mg. of the drug. In the case described below one parenteral dose of 2·5 mg. perphenazine apparently affected the patient for four days. Elsewhere she had at other times received promazine, chlorpromazine, and prochlorperazine without ill effect.

1. *Pediatrics*, 1959, **24**, 739.
2. Asherson, G. L., Broberger, O. *Brit. med. J.* 1961, i, 1429.
3. Nairn, R. C., McEntegart, M. G., Fothergill, J. E., Porteous, I. B. *J. clin. Path.* 1961, **14**, 328.
4. Nairn, R. C. Fluorescent Protein Tracing; chap. 9. Edinburgh. To be published.
5. Weiler, E. *in* Ciba Foundation Symposium on Carcinogenesis: Mechanisms of Action; p. 165. London, 1959.
6. Nairn, R. C., Richmond, H. G., McEntegart, M. G., Fothergill, J. E. *Brit. med. J.* 1960, ii, 1335.

1. Belyavin, G. *J. Hyg. Camb.* 1953, **51**, 492.
2. Broberger, O., Perlmann, P. *J. exp. Med.* 1959, **110**, 657.
3. Boardman, R. H., Fullerton, A., Bethell, M., Conway, S. *Lancet*, 1960, ii, 1450.

A Caucasian woman, aged 32, was given 5 mg. perphenazine (' Fentazin ', ' Trilafon ') for severe tension headache. Two days later she was dysarthric and ataxic, but as it seemed possible that she had taken a double dose of quinalbarbitone the perphenazine was not immediately suspected. Three weeks later she was again given 2·5 mg. parenterally, combined with an analgesic, and for the next four days she had dysarthria, tremor, and an ataxic festinant gait.

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Public Health

CARAVANS CONTENTIOUS

FROM A CORRESPONDENT

THERE must be some deep reasons why caravans should stir peoples' emotions. Perhaps it is an ancient fear for settled communities to worry about what the nomads will bring with them, what they will take away, and what they will leave behind. Perhaps it is bewilderment at an alien pattern of living. Prejudices are deeply rooted and they are here to stay: but so are the caravans. Only bit by bit are we learning to live with them.

The Royal Society of Health has lately discussed the health of permanent caravan-dwellers. The critics of caravans claim that children brought up in them have about $2^1/_2$ times more upper respiratory troubles than children from ordinary homes, and that the incidence of gastroenteritis, sepsis, and accidents is also higher than normal. In adults it is said that mental health suffers with long-continued and unwilling stay in a caravan. The outdoor enthusiasts and the people who make a living out of the caravan industry counterclaim that there is nothing more delightful and healthy than caravanning under ideal conditions. But caravans are used in so many different ways, by so many different people, in so many different places, that any generalisations are apt to be rather misleading.

First there are the touring caravans, never intended for permanent habitation. Some of the hired vans may be in constant use throughout the season by different batches of people who are more carefree in what they do, and how they behave, than the owner himself might be. There is an acknowledged scarcity of caravan sites for the overnight or short-term stay: the site operators have more profit and less bother if they keep their land for the seasonal lettings. The obliging small farmer is beginning to shut his open gate: he sees the eyes of the local planning authority turning upon him, and, worse still, the Inland Revenue to put up his rating assessment and make him add to his income-tax returns. The results of turning away the overnight caravan can be seen in the highway laybys and the roadside verges—insanitary, dangerous, and unpleasant. In many parts of the country the police are taking an increasingly severe line to chase the caravans away from the main roads at night. So the touring caravanner now has to keep a sharp lookout for the very occasional approved overnight stopping-place at a petrol station, or a motel, or else find someone who really wants him.

The permanent touring caravanners are more or less limited to the gypsies, the potters, the tinkers, the showmen, and suchlike traditional wanderers. They bring all their traditional risks as well: not so bad when they come in ones and twos, but overpowering when they gather in their hundreds along the roadside verges for their ancient charter fairs and the horse sales where everything but horses are now sold. All that can be done is for the local authorities to keep their fingers crossed and clean up afterwards.

The static holiday caravan, unhitched by its owner at Easter and towed away in September, has quite another set of hygiene problems. If it is in the corner of a small field for the owner's occasional weekend use, the toilet can cope and the site freshens up with the wind and the weather between his visits. But if he lets it throughout the season to waves of people who are unfamiliar with country life, and the sanitary disciplines of a caravan, the place can soon become dangerously fouled. The visitors do not always have time to get back home within the incubation periods.

A semistatic permanently inhabited caravan is often used by key workers with public works contractors on long-term civil engineering projects, or by skilled tradesmen such as joiners and electricians who want to live with their families on the job. They are all following very good money, and consequently they see themselves equipped comfortably and safely. Much more troublesome and dangerous are those permanent caravanners who are on the run from various forms of local-community oppression. These are the folk who squat with their ramshackle caravans on the common land, the neglected smallholding, or a corner of the refuse tip. They depend too much on what jobs they have clung to in the district to move elsewhere; so they have to lower their standards of living another notch, grumble, and be grumbled at. They are perhaps a social problem first and a public-health problem second.

Sometimes the local authority has to come to the rescue by organising the freelance refugees into some sort of tolerated shanty town, with safer drinking-water, sanitation, and refuse disposal as their basic needs. After that the welfare services have to cope. Sometimes private enterprise organises a better-conducted site for all the socially acceptable caravanners who have the ready money to pay for a higher standard of living. Sometimes these sites are almost luxurious. But when the stage is reached of individually laid-out gardens, sheds, and garages, and obviously no serious intention of moving the caravan for ten years, it might have been better to develop a permanent housing-estate. For those who have to wait their turn for a conventional house, or for those who live in a caravan by choice, the model site is probably nearly as healthy as the real thing.

Isolated permanently inhabited caravans are few. They have their place for the people who need one on account of some physical disease or mental ill health. Sometimes these caravanners can cause peculiar public-health risks, for they are not always easy to deal with: cranks, eccentrics, faddists, and rebels from the togetherness of fashionable community life.

Those who like living in caravans will probably be happy and healthy: those who do not are more likely to be ill. The same could probably be said of people who live in ordinary houses.

Infectious Diseases in England and Wales

Diseases	Week ended June			
	3	10	17	24*
Diphtheria	6	2	4	1
Dysentery	462	510	517	455
Encephalitis:				
Infectious	3	2	1	2
Postinfectious	3	3	2	2
Food-poisoning	163	152	389	257
Measles, excluding rubella	24,325	19,626	18,569	15,864
Meningococcal infection	17	22	19	10
Ophthalmia neonatorum	21	30	7	16
Paratyphoid fever	6	8	5	8
Pneumonia, primary or influenzal	261	249	199	154
Poliomyelitis:				
Paralytic	17	15	14	10
Non-paralytic	8	3	6	4
Puerperal pyrexia	184	155	159	146
Scarlet fever	331	422	420	410
Smallpox	..	..	..	..
Tuberculosis:				
Respiratory	417	403	385	391
Meninges and C.N.S.	6	6	5	7
Other	42	56	57	55
Typhoid fever	1	2	2	3
Whooping-cough	441	488	443	423

* Not including late returns.

Obituary

FREDERICK GREIG HOBSON

D.S.O., D.M. Oxon., F.R.C.P.

Dr. F. G. Hobson, honorary consulting physician to the Radcliffe Infirmary, Oxford, died on June 26, at the age of 69.

From Westminster School he went up to New College, Oxford, in 1910, and took physiology finals in 1914. At the outbreak of war he joined the Army as a motor-cycle dispatch-rider. Thanks to his ability and courage, and an inborne aptitude for applying himself heart and soul to any task he undertook, he was a brigade major with a D.S.O. by 1917, when his military career was ended by orders to go back to England and complete his medical training. He qualified from St. Thomas's Hospital in 1919, and was awarded the Theodore Williams scholarship in pathology. After holding house appointments at Thomas's, he returned to Oxford to do research in Professor Dreyer's laboratory.

In 1922 Hobson was appointed to the staff of the Radcliffe Infirmary as assistant physician. He was also on the staff of Savernake, Wallingford, and Marlborough Hospitals, and had a large private practice, but he played a full part in Oxford medical life—as lecturer and examiner, as a member of boards and committees and of the Oxford Medical Society, the Circle of Willis, and the Medical Club, and as honorary secretary of the Royal Infirmary staff council. In 1933 he was elected F.R.C.P.

A. M. C. writes:

"Hobson was always at work on some medical problem. He was the author of numerous papers, and in 1938 he published *Medical Practice in Residential Schools*, a book which many of his friends believed was written between the hours of midnight and 3 A.M. Through the Oxford Medical Society he organised the collection, processing, and distribution of convalescent measles serum for the protection of children when this was needed.

"His contributions to the life of the Radcliffe Infirmary were many. Generations of registrars, house-physicians, and ward clerks owe him a great debt of gratitude for his example of thorough methods, conscientious medicine, and unfaltering devotion both to his patients and to the ideals of his profession. He knew only one standard, the highest. A man of tireless mental and physical energy, he found time to indulge in his many interests, which included his home and country cottage, sailing boats, carpentry, bird-watching, bee-keeping, and gardening. The generous loan of his country cottage to convalescent colleagues or merely as a holiday resort was characteristic. In 1951 he had a serious illness which left its mark but did not intimidate or deter him. He will long be remembered in Oxford both as a physician and as a man."

Dr. Hobson married Audrey Gotch, daughter of Prof. Francis Gotch of Oxford. She died in 1959, and he leaves two daughters and a son who is also a physician.

RICHARD CONNELL

B.A., M.B. Dubl., F.F.R.

Dr. Richard Connell, honorary consulting radiologist to Cumberland Infirmary, died on June 3 at his home at Wetheral, near Carlisle, at the age of 79.

He graduated, with honours, from Trinity College, Dublin, in 1906, and the following year enlisted in the Navy, where he served with distinction until 1921. During the last four years of his service he was in charge of the department of radiology and electrotherapy at Haslar. In 1921 he settled in Carlisle and soon afterwards he was appointed honorary radiologist to the Cumberland Infirmary, the Dumfries and Galloway Royal Infirmary, and the Workington Infirmary. He soon built up an extensive private practice in the Border district, and he was one of the first doctors to offer a domiciliary radiological service in a rural area, where he had to provide the source of power from his own car. He was elected F.F.R. in 1939. He retired from the hospital service in 1946, but he continued to take an active interest in the medical life of the area.

D. C. and J. S. F. write:

"Dick Connell had the sparkling charm of a 'Kerry gentleman', maintaining his Irish lilt, warmheartedness, and sense of fun to the end. He loved simple things and the quiet pleasures of the countryside. He had a good knowledge of nature and was a keen angler and an entertaining companion on the hills. He kept the hearts of his friends by his integrity, loyalty to his ethics, and his humility about his achievements. He was an incomparable host and a delightful guest, and his friends have treasured memories of evenings spent with him and his wife. He had a large fund of anecdotes, had the happy gift of seeing the fun in incidents, and was a wonderful raconteur.

"He was a devout churchman and was warden at Scotby parish church for twenty years. On his retirement he became a lay reader, so that he might ease the burden of rural incumbents in the area."

Dr. Connell leaves a widow, three daughters, and two sons, Captain R. A. Connell, R.N., and Dr. M. C. Connell, who is a consultant radiologist at Northampton.

Parliament

Regulation of Birth

IN the House of Lords on June 28, Lord BRABAZON of TARA moved that further development and education in the regulation of birth would contribute to world peace. He pointed out that though it had taken two hundred thousand years on this planet to produce a population of 2500 million, it now only took thirty years to add another 2000 million people. Asia, which occupied only a fifth of the land of our planet, had more than half its population and the increase therefore concerned Asia more than any other part of the world. Nature, though anxious about the species, was extremely callous about the individual and ruthless in the extermination of the weak, but knowledge and medical science had sharply lowered the death-rate. In India, for example, the expectation of life was being increased by $2^1/_2$ years every 5 years, and Mr. Nehru had said that some kind of limitation of the growing population was urgent. Lord Brabazon did not believe that men or women really wanted large families, but they would not be deprived of their elemental pleasures simply to avoid overpopulation. Everyone wished the human race to be free, happy, and well fed and it was our duty to make as clear as we could to the world what were the possibilities of population planning.

Lord AMULREE refused to be too upset at the thought of the increase in the population. Although food was distributed badly, more was grown or produced than could be consumed, and there were still many empty spaces in the world which could produce more people, provided that the distribution of food was properly arranged. He was sure that if we saw that those underdeveloped countries which were now making progress got proper food and better education we need not worry about the possibility of dangerous increases of population in the future.

Baroness SUMMERSKILL thought that it was significant that the two generations in which there had been such a spectacular reduction in the time devoted to child-bearing were the first two generations of a literate working class in this country. Social progress was a by-product of economic advance and she believed that this would prove as true in the East as it had in the West. She was sure that Lord Brabazon would command general support if, as a major contribution to peace, he placed the first emphasis on improved economic and educational standards with aid liberally administered *pari passu* with birth control in the vast areas where misery was associated with overpopulation.

The Lord BISHOP of ST. ALBANS, too, thought that we had a responsibility to help the underdeveloped countries. He quoted a Madras doctor who had said "shocking as it may

seem, in many rural areas the cost of having a baby would be cheaper than the price of birth control equipment". This population explosion had not sprung from responsible choice, but had followed medical knowledge. The education which we should bring these countries should be an education in responsibility for parenthood. We should be wide of the mark if we assumed that we only had to export to them a means of family planning widely used in the West. We needed more research into the physiology of reproduction, ovulation, and ways of teaching these things to simple people.

Lord TAYLOR was in favour of the encouragement of the teaching of birth control because it had a lot to do with world prosperity and happiness, but he did not think that there was any evidence that overpopulation had been the cause of modern wars. They were more often due to psychopaths in power and to idiotic nationalistic creeds.

Viscount HAILSHAM, closing the debate in his capacity of Minister of Science, thought that the problem was best discussed objectively as the relationship of population to food supply. He would be astonished if by 2000 A.D. the world population was less than 5000 million. To provide an adequate diet for this number, the world cereal production should be doubled and the production of animal proteins quadrupled. This was a problem which, in his view, was not receiving the attention or action which it deserved. Yet an adequate standard of nutrition for the population of the world was an object at least as worthy of humanity as a space-station on the moon or a trip to Mars.

He believed that the decision whether or not to use any method of birth regulation was an intimate question of personal conduct and conscience. It should not be a matter of social or political pressure in either direction. He was in favour of the existing practice in this country whereby information was available through both Government and private sources, but the means were not (save when genuine health hazards existed) available through the National Health Service at public expense. Since he believed that birth regulation was a matter of social and personal choice, it followed that he was fundamentally opposed to international interference. In his view by far the most fruitful source of action by governments in the immediate future was to concentrate on providing more food for the world.

Legislative Progress

On June 29 the Human Tissue Bill was read a third time in the House of Commons and will now go the the Lords. On June 30 the Public Health Bill, which was introduced in the Lords, received its second reading in the Commons. Lord Amulree's Bill empowering the courts to require blood-tests in affiliation proceedings has completed all its stages in the House of Lords, but it has not won a place in the House of Commons' timetable and will be one of this session's casualties.

QUESTION TIME

Distinction Awards

Mr. KENNETH ROBINSON asked the Minister of Health if he would state, in each of the four categories of award, the numbers of consultants who held teaching hospital appointments and of those who did not.

Mr. ENOCH POWELL replied: The figures for England and Wales are:

—	A plus	A	B	C
*Consultants with teaching hospital contracts	79	216	437	503
Other consultants	9	49	270	910

* Over half these consultants also have contracts with regional hospital boards.

Cancer Research

The total amount spent by the Medical Research Council on cancer research and by the British Empire Cancer Campaign and the Imperial Cancer Research Fund in 1959–60 was about £1,541,400. Of this sum 37·6% was provided from public funds, and 62·4% from voluntary contributions.

Notes and News

ALCOHOLISM

FROM June 12 to 23, 150 participants from some 25 countries attended in Amsterdam the 7th Summer Institute of Scientific Studies for the Prevention and Treatment of Alcoholism. The meeting was attended by representatives of all professions who come into contact with alcoholics—psychiatrists, general practitioners, public-health doctors, social workers, clergymen, sociologists, government officials, lawyers, and police officers. Alcoholics Anonymous had an eloquent spokesman in a Dutch member.

The meeting gained much from the participation of Prof. E. M. Jellinek, whose work over the past twenty-odd years has given a great impetus to work on alcoholism the world over. A lot is nowadays written about the need to integrate research, education, and treatment; but the way to integrate them, said Jellinek, is by avoiding separation of them. He spoke of a Canadian study which showed close correlation between high price of drink and low consumption. He himself had some reservations about this; but other speakers said that elsewhere (e.g., in England, France, and the United States) a similar relationship between high price and low consumption of alcohol had been demonstrated from time to time. Jellinek declared that the drinker learns to expect a reward for drinking—i.e., lowering of tension. He does not learn from the punishment which he receives from drinking: "A horse will not stand this punishment: only man."

Alcoholism was a generic term, the prevalent "species" of alcoholics varying from country to country. The differences between French and Scandinavian/Anglo-Saxon experiences cropped up repeatedly in the discussions. Thus, the French, who are now taking strong measures to educate the public about the dangers of alcoholism, have fixed a level of 1 litre of wine per day as not dangerous, but no other country has adopted a similar precept.

The participants agreed that alcohol abuse is sometimes a significant causal factor in criminality; but the relationship to juvenile delinquency seems more obscure, and a recent Danish study has failed to indicate a clear connection.

Education against abuse of alcohol varies greatly between countries: in Scandinavia it is compulsory, but in other countries it is virtually non-existent. Programmes on alcoholism should be broadcast, particularly to schools. There is need for full information on alcoholism to all interested groups and individuals, possibly on the lines followed in the United States by voluntary councils representing all sections of the community. Information was held to be the most effective means of influencing drinking habits.

Legislation in Norway, Sweden, and Switzerland was regarded as satisfactory: it provided a background threat which encouraged the alcoholic to present himself for treatment. Some believed that means were needed for keeping alcoholics in the institutions so that they could be helped.

PÆDIATRICS AND PSYCHIATRY

To celebrate the visit of the Canadian Pædiatric Society to this country, the British Pædiatric Association mental health committee with the Association of Child Psychology and Psychiatry held a meeting in London on July 1 at which advances of common interest were discussed. Pædiatricians described various ways in which they had developed cooperation with psychiatric colleagues in the care of children at their clinics.

Dr. John Bowlby described the new understanding of the mother-child relationship which has come from studies of animal behaviour; and applications of biochemistry and chromosome studies to work in mental deficiency were reported.

Dr. A. D. B. Clarke (Epsom) spoke of his research during the past ten years on teaching severely subnormal children and adults. The subnormal, given long training, can acquire far more skills and more complex skills than was formerly believed to be possible. Long-term retention of learned skills and transfer of learning have been demonstrated. The subnormal responds well to incentives—including money, prestige, praise, and encouragement to surpass his own achievement. Perhaps the most urgent need at the moment is to find out when to start special training; for it appears that, unlike the normal child, the subnormal learns little spontaneously from his life experiences, and therefore needs special training, and furthermore early teaching apparently has greater results than teaching after early childhood is passed. It even appears that children in hospital achieve more than children at home—perhaps because too little is expected

of the child at home. There is great need to find out how to advise families and training (" occupation ") centres to help these children to learn while they are still small.

EXCERPTA CRIMINOLOGICA

THE Excerpta Criminologica Foundation, in cooperation with the National Council on Crime and Delinquency, are publishing in English this new series of abstracts drawn from journals dealing with criminology and related subjects. Readers who are unable to refer to the original articles may, for a fee, obtain photocopies or translations. The Foundation believe that the *Excerpta* will be of interest to criminologists, criminological institutes, law schools, sociological and psychological institutes, psychiatrists, police authorities, prison administrators, and welfare workers. The chief editors are Prof. T. Würtenberger (Freiburg/Br.), Prof. T. C. N. Gibbens (London), and Prof. W. H. Nagel (Leyden). Six issues will appear each year (annual subscription $30). Copies for the United Kingdom and Commonwealth may be ordered from the Foundation, 67, New Bond Street, London, W.1.

NATIONAL ASSISTANCE BOARD

DURING 1960 the Board's expenditure was about £187½ million (compared with about £157¾ million in 1959), of which more than £166 million was for allowances under the National Assistance Act, 1948, and nearly £11 million for non-contributory old-age pensions.[1]

Of the 1,857,000 allowances 70% were being paid to old people. Sick people and others unable to work—e.g., women with family ties—accounted for about 23%; less than 7% were unemployed and registering for work. Two out of every three recipients were women, mostly widows. The Board consider that among those they help are three small problem groups: men who seem unwilling to work, the unsettled men who frequent reception centres, and men in doubtful health who have a long record of unemployment.

The general fall in the number of allowances to people without work was smaller in this last group. As an experiment arrangements were made in certain areas for the medical examination of men under 55 who had been receiving assistance for six months or more and seemed to have some physical or mental disability (although not registered as disabled persons). Out of 1521 people listed for examination, nearly half found work either before it took place or subsequently. Of the remainder, some were found to be altogether incapable of work, and others to be in need of medical or psychiatric treatment, which was arranged for them. The experiment has now been extended to the whole country.

CENTRAL HEALTH SERVICES COUNCIL

THE Minister of Health, Mr. Enoch Powell, has appointed Sir Russell Brain and reappointed Lord Cohen of Birkenhead, Dr. Annis Gillie, Prof. J. Denis Hill, and Sir Wilfrid Sheldon to the Council for the period ending March 31, 1964. New medical appointments to standing advisory committees are:

Medical.—Dr. T. Lloyd Hughes.
Pharmaceutical.—Dr. W. N. Leak.
Nursing.—Dr. T. Lloyd Hughes (until March 31, 1962).
Tuberculosis.—Dr. L. G. Blair.

MEDICAL RECORD CARDS FOR GENERAL PRACTICE

THE College of General Practitioners has designed record cards which many general practitioners will find useful. The cards will fit into the N.H.S. record envelopes and are distinctively coloured. At present there are available an obstetric-record card; a summary card, on which the principal illnesses, infections, immunisations, and other details may be recorded; and a menstruation chart. These may be had from the secretary of the College of General Practitioners, 41, Cadogan Gardens, London, S.W.3. Also obtainable are sets of language cards, printed in French, Spanish, Italian, German, Hungarian, and Polish, designed to assist in history-taking when doctor and patient have no language in common.

1. Report of the National Assistance Board for 1960. Cmnd. H.M. Stationery Office. 4*s*.

University of London

The following degrees have been awarded:

Ph.D. (in the Faculty of Medicine).—D. M. Shaw, Margaret E. H. Turner Warwick.
M.D.—S. J. Beales, N. S. Capstick, R. H. C. Wells.

University of Liverpool

The following degrees and diplomas have been conferred:

M.D.—R. Finn, R. W. Galloway, R. Harris.
Ch.M.—P. F. Lynch.
M.B., Ch. B.—Jean D. Ames (with first-class honours); D. W. Fielding (with second-class honours); B. R. Anderson, A. K. Boaiety, I. G. Bogle, D. Canter, Ann F. Capey, M. R. J. Claxton, S. B. Cohen, M. Cook, A. Cooper, Sheila M. Cooper, Dolores Corcoran, Josephine C. Corry, F. Cunliffe, E. C. Daniels, Betty Dickinson, Jane Edwards, Georgina A. Ferguson, J. M. Findlay, Marie C. Firth, B. Garston, Pamela M. Hagan, B. V. Harris, Judith A. Heyworth, B. T. Higgins, Joan C. Higgins, J. D. L. Holme, E. W. Humphreys, J. E. Hutson, D. M. Johnston, R. O. Jones, A. P. Kenna, J. M. Kingston, Sheila Lang, T. Langan, Dorothy A. Langton, I. K. Lewkonia, Mary B. Lowe, G. A. McGregor, Janine M. Miller, E. C. Moore, Marjorie Moorhouse, T. M. Murphy, E. G. Parkinson, Aideen D. C. Perry, P. R. Prideaux, A. V. Pullin, Moira Ravey, Anne W. Rees, Patricia M. Ronald, L. Rosenbloom, G. Ryan, Freda Sanderson, A. H. Short, A. Slater, Ethel V. Spence, P. H. Stevens, Annette Tattersall, R. Underwood, Gabriel M. Walsh, K. White, H. G. M. Williams, L. Wilsher, Jean J. Wilson, R. N. Wynn-Williams.
D.P.H.—A. Abdulmawjoud, D. A. Akintonde, J. H. E. Baines, M. A. Bari, N. A. De Heer, A. Griffith, Mahameidevi Gunawardena, W. N. O'Shea, L. J. Perez-Rios, Elizabeth J. Sutton.
D.M.R.D.—H. D. C. Bell, G. H. Evans, S. G. Groves, J. P. Lawson, A. McDermott, I. F. Quayle, Mary C. Wood.
D.M.R.T.—S. M. Masood.

University of Glasgow

Institute of Virology.—Messrs Pfizers, Ltd., have made a grant to this Institute to found a series of lectures to be delivered by scientists from overseas who will be invited to spend 2–3 months at the Institute. Dr. George K. Hirst (New York) will give the first series of lectures this autumn.

University of Dublin

On June 29 the following degrees were conferred:

M.D.—R. C. Gray, Barbara W. M. Partridge.
M.B., B.Ch., B.A.O.—Doreen J. Aucott, W. H. Beesley, T. J. S. Black, C. E. Boursin, R. M. Bridburg, J. E. Cahill, C. J. Condron, J. M. S. Cussen, J. H. Detheridge, K. H. Du Plessis, D. E. Dyer, G. B. R. Fisher, D. J. FitzPatrick, R. M. Galloway, J. E. Gibbon, Anne M. Gillett, W. J. W. Greene, Jane A. W. G. Johnston, V. H. Keely, J. H. M. Lyndsay, M. E. McGrath, Bernardine O'Neill, George Patrikios, M. B. R. Shannon, Rajalingam Sinniah, N. J. Shelley Smith, Timothy Stack, Maria J. Strzelecka, A. O. Williams.
L.M., L.Ch., L.A.O.—D. J. McKay.

Royal College of Surgeons of England

The honorary fellowship of the college has been awarded to Sir Howard Florey, president of the Royal Society and professor of pathology in the University of Oxford, and Dr. Owen H. Wangensteen, chairman of the department of surgery in the University of Minnesota and former president of the American College of Surgeons.

Royal College of Surgeons in Ireland

Mr. C. K. Byrnes has been appointed professor of surgery to the college.

Royal Australasian College of Surgeons

The following office bearers have been elected:

President, Mr. Stanley Wilson, Dunedin; senior vice-president, Mr. Julian Orm Smith, Melbourne; junior vice president, Mr. Kenneth Starr, Sydney; censor-in-chief, Mr. B. K. Rank, Melbourne; hon. treasurer, Mr. C. J. Officer Brown, Melbourne.

British Pædiatric Association

This Association, under the presidency of Prof. A. V. Neale, held a joint annual meeting with the Canadian Pædiatric Society at Cambridge from June 27 to 29. Over 300 doctors, including 50 Canadians, attended. Dr. J. H. Ebbs of Toronto delivered the George Frederic Still lecture. The first awards of the James Spence medal were made to Prof. Alan Moncrieff and Prof. R. A. McCance.

At the annual business meeting of the Association the following were elected to office for 1961–62:

President, Prof. Alan Moncrieff; president elect, Dr. C. F. Harris; treasurer, Prof. A. G. Watkins; and secretary, Dr. E. W. Hart.

Royal Institution

Prof. R. J. Harrison has been elected Fullerian professor of physiology in succession to Prof. J. Z. Young.

Council for Professions Supplementary to Medicine

The medical members of this Council, which has been set up under the Act of 1960, are: Prof. Roland Barnes, Prof. J. McClure Browne, Dr. H. A. Burt, Dr. J. D. Cameron, Dr. G. A. Clarke, Dr. J. O. F. Davies, and Prof. D. W. Smithers. The chairman is Sir Sydney Littlewood.

British Diabetic Association

A meeting of the medical and scientific section of this Association will be held on Sept. 29 and 30 in Birmingham, when the programme will include a symposium on diabetic renal disease. Further particulars may be had from the secretary of the section, 152, Harley Street, London, W.1.

The Association of Anæsthetists of Great Britain and Ireland

Research essay prizes for 1961 have been awarded to Dr. J. D. Robertson, Dr. A. Wynn Williams, Dr. A. C. Forrester, Mr. J. Brown, and Mr. D. G. Calvert. Regulations for the 1962 prizes can be had from the honorary secretary of the Association at 47, Lincoln's Inn Fields, London, W.C.2.

Chest and Heart Association

This Association, with the cooperation of the Federal Government of Nigeria and at the invitation of the University College of Ibadan, is sponsoring a health and tuberculosis conference to be held in Ibadan from March 26 to 31, 1962. Further particulars may be had from the conference secretary of the Association, Tavistock House North, Tavistock Square, London, W.C.1.

Society for Relief of Widows and Orphans of Medical Men

On Dec. 31, 1960, 23 widows were in receipt of grants from this society. During 1960 one widow died at the age of 98, who had received grants since 1914. The total amount distributed during the year from the ordinary and Brickwell funds was £4205.

Membership is open to male registered medical practitioners who, at the time of election, are living within twenty miles of Charing Cross. Inquiries should be addressed to the hon. secretary, Dr. J. A. Struthers, at 11, Chandos Street, London, W.1.

Domiciliary Midwifery

On Wednesday, Oct. 18, the Royal College of Obstetricians and Gynæcologists is holding a symposium on this subject which has been arranged with the College of General Practitioners.

The theme of the morning session will be the avoidable factor in maternal mortality, and there will be discussions on the selection of cases for domiciliary confinement, the toxæmias of pregnancy, hæmorrhage, and the place of the flying-squad. The speakers will be Sir John Peel, Prof. T. N. A. Jeffcoate, Mr. Arnold Walker, and Mr. Frank Stabler. The subject chosen for the afternoon session is the staffing and management of a general-practitioner/obstetrician unit and the part it should play in the obstetric services. The opening speakers will include Mr. John Stallworthy, Mr. R. A. Tennant, Dr. T. Maurice, and Dr. P. B. Bailey. Though the meeting is intended primarily for general practitioners who hold the D.OBST., as far as space allows it will be open to all doctors who wish to attend. Applications should be sent before Oct. 4 to the secretary of the college, 27, Sussex Place, Regent's Park, London, N.W.1.

The papers and discussions of the Mental Health Services Conference, held under the auspices of the Royal Institute of Public Administration at Peebles last March, have now been published. Copies (5*s*.) may be had from the hon. secretary of the Edinburgh and East of Scotland Regional Group, 20, Cockburn Street, Edinburgh, 1.

Surgeon Rear-Admiral D. D. Steele-Perkins has been appointed honorary surgeon to the Queen in succession to Surgeon Rear-Admiral G. Phillips, and Surgeon Captain A. D. Petro honorary physician to the Queen in succession to Surgeon Captain P. de B. Turtle.

Air Vice-Marshal Nelson, O.B.E., has been appointed honorary physician to the Queen.

Mr. H. S. Taylor-Young is to succeed Major A. C. White Knox as surgeon-in-chief of the St. John Ambulance Brigade. Major White Knox is retiring after more than fifty years' work for the first-aid movement.

A meeting of the Biochemical Society will be held on Thursday and Friday, July 13 and 14, beginning at 10.40 A.M. on Thursday, in the department of biochemistry, University of Oxford. The programme will include a colloquium on the training of biochemists.

A symposium on chest diseases in children is to be held at Whittington Hospital Archway Wing, Archway Road, London, N.19, on Wednesday, July 26, at 11.30 A.M. The speakers will be Dr. Edwin L. Kendig, Jr. (Richmond, Virginia), Dr. Warren S. Chernick (Philadelphia), and Dr. L. B. Strang.

A committee meeting of the Group for Representation of the Views of Clinical Psychiatrists will be held on Thursday, July 13, at 5.30 P.M., at Tavistock House North, Tavistock Square, London, W.C.1.

The Ministry of Health's *Hospital Building Notes* no. 19 gives guidance on the design of a medical photography and medical illustration department for general hospitals, including teaching hospitals. A photographic department will normally be needed for a hospital or group of hospitals of over 400 beds, and in smaller hospitals, where there are important specialist units, a department may occasionally be justified. Copies (1*s*. 6*d*.) may be had from H.M. Stationery Office.

A correspondent has unbound back numbers of *The Lancet* from 1943 to 1953 which he would like to give to the library of one of the new Commonwealth medical schools. The issues are at present in Hampstead, and the library would have to arrange packing and transport. Further particulars may be had from *The Lancet* office.

CORRIGENDUM: *Bad Cheese.*—The cheese referred to in our issue of June 24 (p. 1411) was contaminated with staphylococci, not streptococci.

Diary of the Week

JULY 9 TO 15

Tuesday, 11th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Rev. A. T. Welford: Changes of Performance with Age. (F. E. Williams lecture.)

SOCIETY FOR THE STUDY OF ADDICTION
8 P.M. (11, Chandos Street, W.1.) Dr. M. M. Glatt: Role of the Recovered Alcoholic in Furthering Education Regarding Alcoholism.

Wednesday, 12th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. G. W. Milton: Behaviour of Gastric Epithelium under Various Conditions. (Hunterian lecture.)

EXPERIMENTAL RADIOPATHOLOGY RESEARCH UNIT
2 P.M. (Wolfson Institute, Hammersmith Hospital, Ducane Road, W.12.) Dr. Konrad Bloch (Harvard University): Studies on Lipid Biosynthesis.

Friday, 14th

ROYAL COLLEGE OF SURGEONS OF EDINBURGH, Nicolson Street, Edinburgh, 8
3.30 P.M. Prof. R. Milnes Walker: Aspects of Liver Disease.

Appointments

CUMMING, PATRICIA M., M.B. Aberd., D.P.H.: M.O.H. and assistant school M.O., Banff.

RAYMOND, SYLVIA J. A., M.B. Manc., D.C.H.: assistant M.O.H. and school M.O., Bolton.

SHAW, F. O. J., M.R.C.S.: deputy M.O.H., Dover.

STEVENS, J. D., M.D. Lond., M.R.C.P.: consultant physician, Mexborough area.

Cornwall County Council:

JENKINS, MAIR L., M.B. Wales: school M.O., Cornwall.

MYHILL, M. D. H., B.M. Oxon., D.P.H.: school M.O., Cornwall.

PATTERSON, ISOBEL R. S., M.B. Aberd., D.P.H.: school M.O., Cornwall.